MATCHING DRY EYE TREATMENTS TO PATIENT TYPE

This author divides patients into three types and treats accordingly.

BY RICHARD L. MAHARAJ, OD, FAAO

The past decade has seen an increase in treatment options for the management of patients with dry eye disease (DED). Several therapeutics have been FDA-approved specifically for DED, and multiple in-office treatment devices have made it to the marketplace with varying availability in the United States and Canada. Globally, the estimated DED market will reach $5 billion by 2023,[1] so staying abreast of what is available will be key to the successful DED specialist.

The growing interventional DED toolkit requires a deeper understanding of each option's mechanism of action and recognition of which patients are the best candidates for each. I tend to divide patients into different patient types to guide my choice of these current and emerging treatment options.[2]

THE EPISODIC PATIENT

The core mechanism for DED is evaporative stress, and there is no shortage of triggers lately: increased screen time, chronic mask use resulting in air blowback (mask-associated DED), and cosmetic ocular offenders, just to name a few.[3-5] The episodic patient will experience five to six flare-ups per year, but two tools can help to reduce the frequency and severity of these episodes.[6]

HA-Based Lubricant Drops

Hyaluronate (HA)-based lubricants exhibit non-Newtonian properties, allowing them to maintain higher viscosity when the eye is open and reduced viscosity when exposed to shearing forces during active blinks.[7] A recent rheological analysis of commercial lubricants revealed three groups exhibiting distinct degrees of viscoelasticity. The key in choosing an HA drop is to pick one with optimal shear-thinning properties with blink acceleration and high residence time and clarity at blink intervals for clear vision. In one study, iDrop MGD (I-MED Pharma) exhibited optimal HA characteristics that can translate to better dynamic performance by decreasing evaporative triggers of stress.[7]

A New Steroid Option

If a patient is having an active flare, the recently FDA-approved loteprednol etabonate ophthalmic suspension 0.25% (Eysuvis, Kala Pharmaceuticals) is an on-label option to manage both signs and symptoms of DED for short-term (up to 2 weeks) use. The STRIDE study showed symptomatic improvement in as early as 2 days of use, with 0.6% of treated patients experiencing a posttreatment IOP increase of 5 mm Hg.[8] When lubricant drops fail

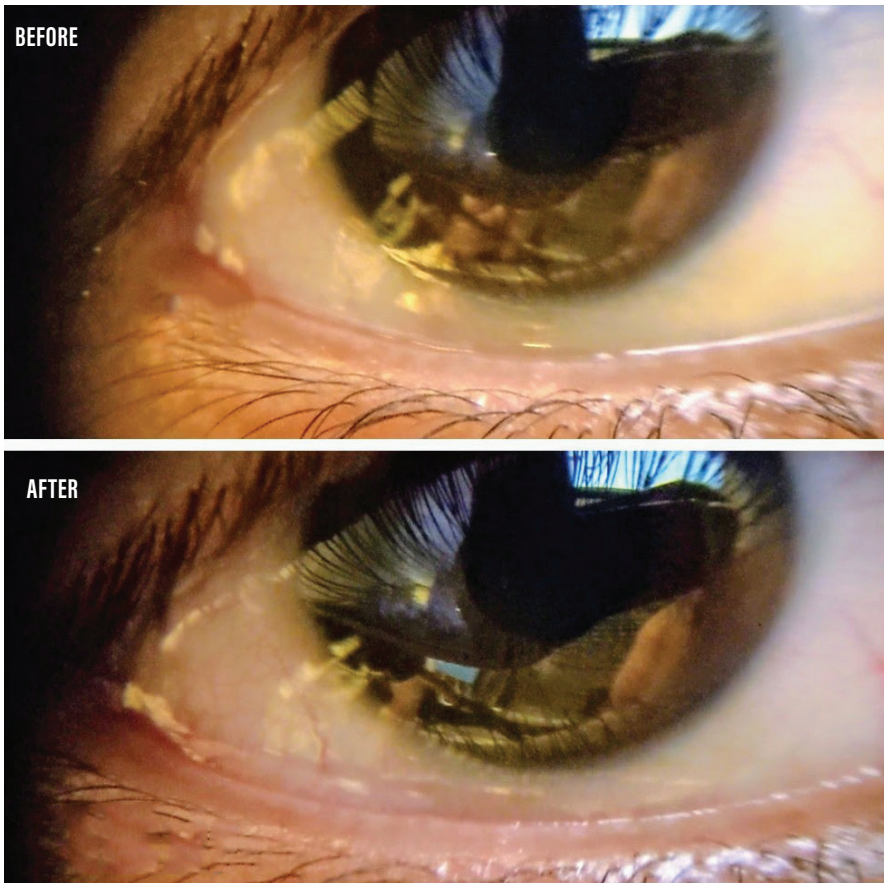

Photo courtesy of @dryeyejedi

Figure 1. Tear volume is visibly increased with use of the iTear100, shown here with a 2.5-fold thickening of the tear meniscus height.

to sufficiently suppress tear-related inflammation, this steroid is an effective first-line option.

What's New?

We know that the lacrimal functional unit can underperform given the aforementioned lifestyle triggers. A nondrop option may be appealing to many patients from a convenience perspective. The iTear100 (Olympic Ophthalmics) is an externally applied neurostimulation device that targets the neurosensory component of tear homeostasis. The device stimulates the external branch of the anterior ethmoidal nerve on the lateral aspect of the upper nose with a twice-daily dosing schedule for 30 days. The stimulation of the nasolacrimal reflex results in a statistically significant improvement in meibomian gland expression, tear breakup time, and corneal and conjunctival staining (Figure 1). In short, the entire lacrimal functional unit improves, which correlates to improvements in signs and symptoms.[9]

THE CHRONIC PATIENT

When nine out of 10 patients with DED have a meibomian gland disease (MGD) component, it should come as no surprise that eyelid hygiene contributes greatly to the success of the patient with chronic DED.[10] I have found the two treatment options described below to be reliable and effective for treatment and maintenance of the chronic patient.

ZEST

The Zocular Eyelid System Treatment (ZEST, Zocular) leverages an extract of *Abelmoschus esculentus*, commonly known as okra, used along with microblepharoexfoliation to remove biofilm and manage *Demodex*. A single treatment decreases matrix metallopeptidase 9 and reduces the use of rewetting drops for contact lens patients.[11] This polysaccharide exerts anti-demodectic, antibacterial, and antiinflammatory effects on the soft tissues of the lid margin.[12] Preventive care with a semiannual ZEST protocol has become integral to the success of many of our patients.

IPL

Intense pulsed light (IPL) therapy gives DED specialists a tool with which to target a diverse range of vasogenic, microbial, and inflammatory contributors to MGD (Figure 2).[13] Patient candidacy is limited to those with Fitzpatrick skin types I-IV, but IPL provides results that these patients can feel and see. In addition to changes in signs and symptoms, IPL improves the microstructure of the glands, which is measurable on confocal microscopy.[14] The OptiLight (Lumenis) is a new FDA-approved IPL option specifically labeled for treating MGD.

What's New?

Radiofrequency (RF) energy has a long history in skin rejuvenation and cosmetic procedures. The application of RF heat to the eyelid to induce meibum liquefaction and potentially enhance meibomian gland neural stimulation is being studied.[15] Jaccoma et al found improvements in signs and symptoms in patients treated with RF energy compared with patients treated using the LipiFlow Thermal Pulsation System (Johnson & Johnson Vision) 1 month after treatment.[16] Recently, a two-step approach using RF energy to treat both MGD and conjunctivochalasis electrosurgically yielded clinical improvement in a wide array of patient subtypes.[17] The added cosmetic effect of reduced rhytides

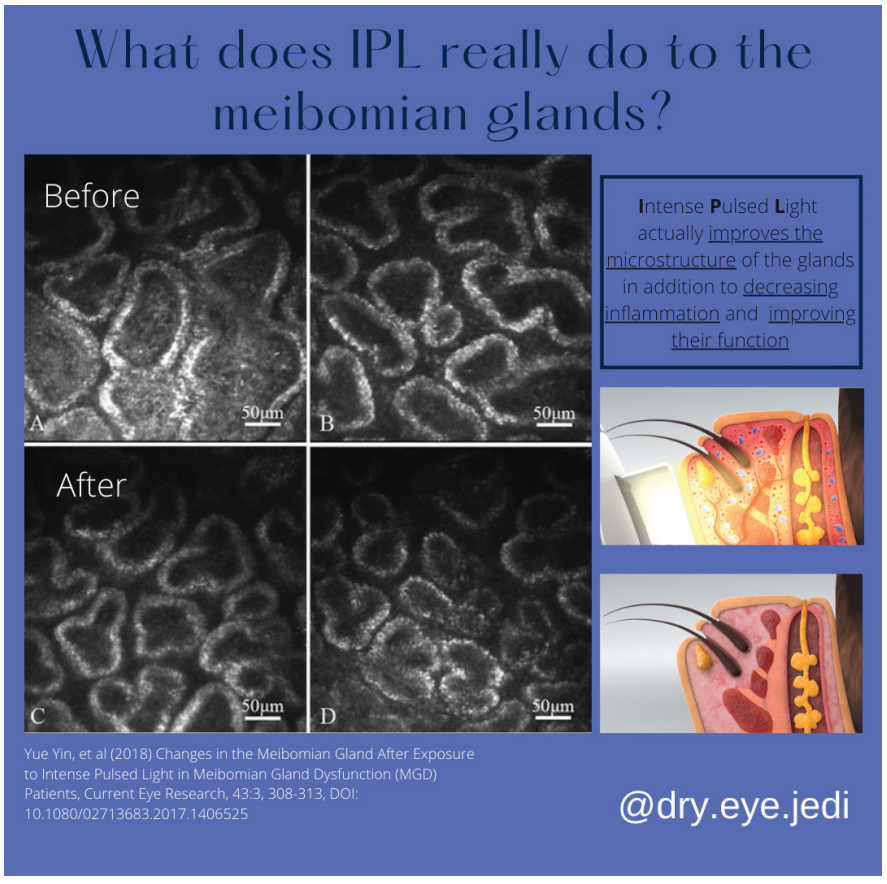

Figure 2. IPL exerts a therapeutic effect on the microstructure of the meibomian glands in addition to improving their function and decreasing inflammation.

and improved microanatomic eyelid apposition makes RF an emerging player in the MGD treatment space.

THE REFRACTORY PATIENT

The patient with severe DED needs all hands on deck. In addition to the treatment modalities described above, patients with DED and severe epitheliopathy, filamentary keratitis, and neurotrophic keratopathy require a pivot to step 3 and 4 treatment options, as outlined by the Tear Film and Ocular Surface Society's Dry Eye Workshop II.[18] Specifically, blood-based treatments such as autologous serum eye drops and platelet rich plasma (PRP) can help to relieve these patients. Autologous serum eye drops and PRP are tools I find myself reaching for more often for patients with complex OSD, particularly when certified staff can prepare them in-house.

Autologous Serum Eye Drops

Autologous serum eye drops are prepared using blood drawn from the patient. The component of blood that remains after clotting is centrifuged, filtered, and prepared with saline to a specific concentration. The preparation is rich in epidermal, fibroblast, and nerve growth factors, among others, all of which can increase epithelial proliferation and healing and decrease inflammation. Autologous serum eye drops also contain transforming growth factor beta, which can decrease stromal transparency. Therefore, concentrations are often kept to 20%,[19] although concentrations of up to 100% have been used with no adverse effects reported.[20] Autologous serum eye drops are effective for treating OSD associated with graft-versus-host disease, Sjögren syndrome, and neurotrophic keratopathy refractory to conventional therapy.[20]

PRP

PRP differs from autologous serum in that the drawn blood is prevented from clotting and a series of centrifugation steps is used to separate the PRP from the blood cells. PRP contains higher concentrations of growth factors than autologous serum eye drops, and as such it can have an enhanced effect on epithelial healing. In addition to the conditions listed above, recurrent corneal erosions and persistent epithelial defects respond well to PRP.[20] There is evidence that PRP significantly increases subbasal nerve plexus density as well, suggesting a possible pathway to managing patients with corneal neuropathic pain.[21] The ability to prescribe the exact concentration of growth factors in PRP gives the practitioner a controlled, potent, but natural option for refractory cases.

What's New?

Because blood-based products in eye care are not regulated, their preparation and consistency are heterogeneous. AlloTears (Allotex) is being developed as an allogenic option for serum tears that may reduce barriers to accessing autologous serum eye drops consistently and safely.

IT'S NOT ALL BLACK AND WHITE

The multifactorial nature of DED requires us to diversify our treatment portfolios. See *Treatments on the Horizon* for a look at additional treatment options not discussed here that are in the development pipeline.

Remember that the chronic patient can be episodic and that the refractory patient is inherently

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TREATMENTS ON THE HORIZON

OC-01

OC-01 (varenicline, Oyster Point Pharma) is a highly selective nicotinic acetylcholine receptor agonist being developed as a preservative-free nasal spray to treat the signs and symptoms of DED. With OC-01, Oyster Point is looking to leverage the parasympathetic nervous system, which controls tear film homeostasis partially via the trigeminal nerve, accessible within the nose, to promote natural tear film production and to reestablish tear film homeostasis. OC-01 is an investigational drug and has not been approved for use in any country.[1] Its safety and efficacy have yet to be established.

AR-15512

AR-15512 (AVX-012, Aerie Pharmaceuticals) is an investigational eye drop in clinical development as a potential treatment for dry eye that, according to the company, may improve both symptoms and signs of the disease. The active ingredient in AR-15512 is a proprietary small-molecule selective agonist of the transient receptor potential melastatin 8 cold thermoreceptor, which is a novel therapeutic target for dry eye. Top-line results from a large phase 2b study evaluating the safety and efficacy of AR-15512 in patients with DED are expected later this year.[2]

Reproxalap

Reproxalap (Aldeyra Therapeutics) is a novel small-molecule drug candidate for reducing ocular inflammation in DED by inhibiting reactive aldehyde species (RASP), which are elevated in a variety of inflammatory diseases. Topical reproxalap has been studied in more than 1,100 patients thus far with no observed safety concerns. In a phase 2b clinical trial, reproxalap demonstrated broad activity across a variety of symptoms and signs in patients with DED.[3] The company intends to advance 0.25% topical ocular reproxalap, its lead RASP inhibitor, for the treatment of DED.

SkQ1 Eye Drops

SkQ1 (Visomitin, Mitotech) is a small molecule purposely developed to deliver the highly active antioxidant plastoquinone into mitochondria. Visomitin is a topical formulation of SkQ1 that has been developed to target dry eye syndrome, uveitis, and age-related macular degeneration. The company reported positive results of a phase 3 clinical study in February and is targeting new drug application submission to the FDA in 2022.[4]

Minocycline Ophthalmic

Hovione recently announced the successful completion of a phase 2 clinical trial of minocycline (Meizuvo; contingent brand name), an acne drug repurposed for ophthalmic administration and targeting meibomian gland dysfunction (MGD).[5] It is a preservative-free formulation enabled by the company's proprietary minocycline base, which is stabilized as a microparticle in a novel vehicle. The phase 2 study included 270 patients with dry eye caused by MGD and tested two strengths of the ophthalmic formulation of minocycline against a vehicle in a 1:1:1 randomization. Both formulations of minocycline were safe and well tolerated, with less than 3% of patients reporting blurring vision or eye irritation.

1. OC-01. Oyster Point. oysterpointrx.com/pipeline/oc-01/. Accessed June 23, 2021.
2. Ocular surface disease. Aerie. aeriepharma.com/rd/ocular-surface-disease/ar-15512/. Accessed June 23, 2021.
3. Reproxalap: phase 2b dry eye disease results. Aldeyra Therapeutics. September 2018. www.aldeyra.com/wp-content/uploads/2019/08/Aldeyra-Therapeutics-Announces-Positive-Results-from-Phase-2b-Dry-Eye-Disease-Clinical-Trial.pdf. Accessed June 23, 2021.
4. Mitotech and Essex Bio-Technology announce positive results of VISTA-2 phase 3 clinical study in dry eye disease [press lrelease]. Mitotech. February 26, 2021. www.mitotechpharma.com/news/mitotech-and-essex-bio-technology-announce-positive-results-of-vista-2-phase-3-clinical-study-in-dry-eye-disease/. Accessed June 23, 2021.
5. Hovione completes its phase 2 clinical trial of the first minocycline ophthalmic [press release]. Hovione. March 17, 2021. www.hovione.com/press-room/press-release/hovione-completes-its-phase-2-clinical-trial-first-minocycline-ophthalmic. Accessed June 23, 2021.

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chronic. In other words, treatments do not exist in discreet silos. Over my past decade of specializing in this rapidly evolving field of treating patients with DED, interventional rather than reactive management strategies using new and emerging treatment options have allowed me to connect the necessary empathy my patients require to therapeutic precision. ■

1. Global dry eye medication market report: 2020: market is expected to recover and reach $5.1 billion in 2023 – forecast to 2030. *GlobeNewswire*. February 15, 2021. www.globenewswire.com/fr/news-release/2021/02/15/2175300/28124/en/Global-Dry-Eye-Medication-Market-Report-2020-Market-is-Expected-to-Recover-and-Reach-5-1-Billion-in-2023-Forecast-to-2030.html. Accessed June 9, 2021.
2. Karpecki PM, Prokopich CL, Racine L, et al. Dry eye diseases and ocular surgery: practical guidelines for Canadian eye care practitioners. *Can J Optom*. 2017;79(4):19-33.
3. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II pathophysiology report. *Ocul Surf*. 2017;15(3):438-510.
4. Moshirfar M, West WB, Marx DP. Face mask-associated ocular irritation and dryness. *Ophthalmol Ther*. 2020;9(3):397-400.
5. Periman LM, O'Dell LE. When beauty doesn't blink. *Ophthalmology Management*. 2016;20: 27,32,34,36,46.
6. 2020 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc.
7. Arshinoff S, Hoffman I, Nae H. Rheological behavior of commercial artificial tear solutions. *J Cataract Refract Surg*. 2021;47(5):649-654.
8. Holland E, Nichols K, Foulks G, Gupta P. Efficacy and safety of KPI- 121 0.25% for short term relief in dry eye (STRIDE). Poster presented at: American Society of Cataract and Refractive Surgery Virtual Annual Meeting; May 16-17, 2020.
9. Ji MH, Moshfeghi DM, Periman L, et al. Novel extranasal tear stimulation: pivotal study results. *Trans Vis Sci Tech*. 2020;9(12):23.
10. Lemp M, Crews L, Bron A, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea*. 2012;31(5):472-478.
11. Narayanan S, Kasraie N, Stewart M, et al. Lid margin debridement improves contact lens discomfort caused by meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2019;60(9):6368.
12. Wenting L, Gong L. Anti-demodectic effects of okra eyelid patch in Demodex blepharitis compared with tea tree oil. *Exp Ther Med*. 2021;21(4):338.
13. Suwal A, Hao J, Zhou D, Liu X, R. Suwal and C. Lu, Use of intense pulsed light to mitigate meibomian gland dysfunction for dry Eye disease. *Int J Med Sci*. 2020;17(10):1385-1392.
14. Yin Y, Liu N, Gong L, Song N. Changes in the meibomian gland after exposure to intense pulsed light in meibomian gland dysfunction (MGD) patients. *Curr Eye Res*. 2018;48(3):308-313.
15. Johnson SM. Sublative radiofrequency improves skin texture and improves dry eyes. *Practical Dermatology*. 2019;15(3):44-45.
16. Jaccoma E, Litherland C, Jaccoma A, Ahmed A. Pellevé vs Lipiflow MGD-Related Dry Eye Treatment Study: The ThermaLid Procedure. *Journal of Dry Eye Disease*. 2018;1(1):e11-e21.
17. Nguyen L, Jaccoma E. Treatment for conjunctivochalasis: a combined approach utilizing radiofrequency cauterization and thermalid procedure. *Journal of Dry Eye Disease*. 2021;4(1):e1- e11.
18. Jones L, Downie L, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628.
19. Pan Q, Angelina A, Marrone M, Stark W, Akpek E. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev*. 2017;2:CD009327.
20. Bernabei F, Roda M, Buzzi M, Pellegrini M, Giannaccare G, Versura P. Blood-based treatments for severe dry eye disease: the need of a consensus. *J Clin Med*. 2019;8(9):1478.
21. Fea A, Aragno V, Testa V, et al. The effect of autologous platelet lysate eye drops: an in vivo confocal microscopy study. *Biomed Res Int*. 2016;2016:8406832.

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