

Current Questions in Dry Eye Therapy

Managing dry eye disease (DED) can be a challenge, and treatment is an inexact science, even in light of the well-vetted DEWS II treatment recommendations. In addition, consider how rapidly the field of dry eye is evolving—the surprising DREAM study results came out last year, and new therapeutics are hitting the market at a brisk pace. As ophthalmologists question how to integrate new developments, drugs, and devices into practice, some insights from dry eye experts may be helpful.

Why Is DREAM Important?

In May 2018, much-anticipated study results from the Dry Eye Assessment and Management (DREAM) Study Research group showed that there was no benefit of omega-3 over placebo in treating either signs or symptoms of DED.¹ “I was blown out of the water to see that the results were not even a little bit positive for omega-3, since prior studies did show some benefit,” said Giacomina Massaro-Giordano, MD, at the University of Pennsylvania in Philadelphia—one of the dry eye specialists involved in the study.

What sets the DREAM study apart. DREAM was the largest study of omega-3 supplementation for DED worldwide and used the highest dose of omega-3, said Penny A. Asbell, MD, FACS, at the University of Tennessee

Health Science Center in Memphis. The study tested 3,000 mg fish-derived omega-3 fatty acid in triglyceride form versus a placebo of 1,000 mg refined olive oil. It included typical DED patients from practices across the United States; all had signs and symptoms of moderate to severe disease and were allowed to use concurrent DED therapies. By contrast, other studies have been small and/or very specific in terms of population, such as studies done in India, where diet is significantly different.¹

Heterogeneous group. Although Dr. Massaro-Giordano described DREAM as well designed, she pointed out how difficult it is to see a significant treatment effect in a disease as heterogeneously defined as DED. Dr. Asbell, the principal author of the DREAM study, noted that the study included a heterogeneous group of patients, varying in terms of Ocular Surface Disease Index (OSDI) scores, conjunctival and corneal staining scores, tear break-up times, and Schirmer test results, etc. However, the researchers found no beneficial effect of omega-3 supplementation in the many subgroups based on degree of symptoms, severity of signs, level of omega-3 in the blood at baseline, and presence of specific diseases associated with DED.

Olive oil effect. Dr. Massaro-Giordano noted another possibility: It’s not that omega-3 didn’t have a positive



TREATMENT. Dr. Shen uses IPL to treat a patient with MGD.

effect but that the control—olive oil—may also have had a beneficial effect. After all, the study showed that 54% of control patients and 61% in the study group had a 10-point or greater improvement in OSDI outcomes.¹ However, Dr. Asbell noted that DREAM researchers carefully examined the possibility of a beneficial effect of their olive oil placebo, but they found an effect implausible. The dose of olive oil was approximately 1 teaspoon a day, and it was refined, lacking the polyphenols in extra virgin olive oil that are believed to provide beneficial effects in other conditions.¹ “The severity of nearly all signs in both treatment groups was essentially unchanged from baseline levels over the year of the study,” said Dr. Asbell. The only large change was in symptoms, and it was identical in both groups, consistent with the placebo

BY GABRIELLE WEINER, MS, CONTRIBUTING WRITER, INTERVIEWING PENNY A. ASBELL, MD, FACS, GIACOMINA MASSARO-GIORDANO, MD, JOANNE F. SHEN, MD, AND SONAL S. TULI, MD, MED.

effects seen in other DED trials.

Dr. Massaro-Giordano said, “We don’t know if olive oil has a positive effect, as there may be a substance in it that we can’t measure. Yes, it’s only 1 teaspoon a day, but it’s still something.” She added, “It’s possible we didn’t see a better effect because the ‘purification’ process of the omega-3 may be different from what has been studied previously.”

What to tell patients. “A lot of patients have heard the hype about omega-3 and gravitate toward it because they like the idea of using something natural,” said Sonal S. Tuli, MD, MEd, at the University of Florida in Gainesville. She tells patients about the lack of randomized controlled trials to support the effectiveness of omega-3 and the strong placebo effect observed in many dry eye studies. Still, she said that she sees little harm in patients trying omega-3 supplements. Moreover, several studies demonstrate positive effects of omega-3 fatty acids on other organs (e.g., the heart, lungs, and skin), which could benefit the patient even if there is no effect on their dry eyes. So, if a patient asks for advice on which omega-3 to try, she tells them to buy the triglyceride formulation (1 g/day).

In the past, Dr. Massaro-Giordano advised patients to take fish oil. “Not anymore. Now I explain all the studies, including the most recent DREAM results.” Some patients ask, “Could olive oil have a benefit?” To them, she says, “If you want to, try the olive oil. If you can afford a good purified fish oil, high in EPA and DHA, go for it.”

“Omega-3 appears to be safe,” said Dr. Asbell, “but, for any treatments, look for quality evidence, such as randomized controlled trials, before you believe in their ability to ‘cure.’”

What Do Users of LipiFlow and IPL Have to Say?

LipiFlow Thermal Pulsation System (Johnson & Johnson Vision) and intense pulsed light (IPL) represent two instruments for expressing meibomian glands that are clogged with waxy deposits in patients with meibomian gland dysfunction (MGD). While some clinicians believe that warm compresses and lid

scrubs are just as effective as the more expensive systems, said Dr. Massaro-Giordano, “That’s not quite correct. There is a head-to-head study² showing that LipiFlow is more effective than warm compresses, but success rates depend heavily on choosing the correct candidates. It works best for posterior blepharitis patients whose meibomian glands aren’t scarred down.”

LipiFlow for mild to moderate MGD. LipiFlow, FDA approved in 2011, consists of an inner shield that slides beneath the lids and over the globe, emitting heat out toward the lids to liquify the meibum. An air bladder sits on the eyelid and massages the lid to open the glands and express the liquified meibum. The design of the device protects the cornea and the globe from the heat and pressure created by the system. The treatment takes about 15 minutes.

The Mayo Clinic in Arizona acquired LipiFlow in 2012, said Joanne F. Shen, MD, who practices there. “When I first started in 2012, I followed the manufacturer’s protocol, but 50% of my dry eye patients were returning dissatisfied, saying that the treatment didn’t work and requesting their money back. I spent a lot of time doing service recovery. My patients who could afford it were averaging 75-80 years old and had MGD for 40-plus years. Since then, Level I evidence has been published showing that LipiFlow is effective in patients with a mean age of 50-66.”³⁻⁶

More affordable. Now the wholesale prices of the actuators (the inner heating shield) have dropped, enabling many centers to offer LipiFlow at more affordable prices, said Dr. Shen. Its advantages are that it treats both the upper and lower lids and is extremely well tolerated, she said. “I have patients who definitely improve symptomatically and clinically on exam with LipiFlow, but the benefits require retreatment every three to 12 months, and it doesn’t work on everyone.”

Dr. Shen pointed out that the associated diagnostic module, LipiView II Ocular Surface Interferometer, is able to detect partial blinks, and this helps her identify good candidates who are likely to respond. Specifically, she said,

“Simply expressing the meibomian glands may not lead to improvement if a patient isn’t blinking fully, especially in Arizona’s dry climate.”

IPL for severe MGD. For more severe DED, Dr. Shen may turn to IPL, which is used by dermatologists to treat rosacea, acne, and sun damage. IPL followed by meibomian gland expression for treatment of dry eye in ocular rosacea patients was discovered and popularized by Rolando Toyos, MD, an ophthalmologist based in Memphis, Tennessee.⁷ The mechanism of action has not been proven but its efficacy has been hypothesized to be due to powerful bursts of light at specific wavelengths to alter blood vessels near the surface of the skin to alleviate inflammation, minimize bacteria on the skin and eyes, and possibly reduce oxidative stress, all of which may have a beneficial effect on MGD.⁸ Typically, it is only used when the patient has run out of options, said Dr. Shen.

Patient selection. “If a patient has rosacea and their main concern is eye redness, I recommend IPL,” Dr. Shen said. For these cases, she said that IPL and meibomian gland expression can be more helpful than LipiFlow. Controlled prospective studies from Asia have shown a significant advantage of IPL in improvement of symptoms and meibum quality.⁹⁻¹² Dr. Massaro-Giordano added that she finds IPL helpful for any patient with severe lid disease whose glands are still active. She reports a success rate for IPL that can range from 40%-60% in the right patients.

Considerations. Because IPL can be painful, Dr. Shen will often try LipiFlow first, especially if a patient has a high sensitivity to pain. Dr. Massaro-Giordano uses lower IPL settings for patients with MGD (instead of the setting used for acne and rosacea in the dermatologist’s office). Her patients haven’t found it to be all that painful, she said.

Theoretically, said Dr. Shen, “after you have their glands open and the patients feel a little better, you should be able to transition to LipiFlow.” So far, though, she has not been able to wean her successful IPL patients to LipiFlow. “Many patients are fearful that a change in treatment plan might derail their

improvement,” she said.

Although Dr. Massaro-Giordano uses IPL before LipiFlow successfully, she noted that you can't use IPL in patients with heavily pigmented skin. Dark skin absorbs the light from IPL and the skin can heat up, leading to inflammation or hyperpigmentation, she said. Thus, she recommends LipiFlow for these patients.

Alternatives. Dr. Shen said, “I do a series of four to test whether the patient will respond. If treatment is unsuccessful, we focus instead on protective mechanisms to sequester the firing of the corneal nerves with goggles or scleral lenses, cocooning the ocular surface from the environment.” If a patient can't afford LipiFlow or IPL, warm compresses and eyelid scrubs are still helpful, Dr. Massaro-Giordano noted.

“We don't know exactly why IPL works,” said Dr. Shen. “Yes, there may be a psychological component, but I have definitely seen patients' conjunctival redness get better along with

some other signs and symptoms.” Dr. Massaro-Giordano added that although preliminary studies of IPL show positive results, more research is needed.

1 Asbell PA et al, for the Dry Eye Assessment and Management Study Research Group. *N Engl J Med.* 2018;378(18):1681-1690.

2 Blackie CA et al. *Clin Ophthalmol.* 2016;10:1385-1396.

3 Yeo et al. *Invest Ophthalmol Vis Sci.* 2106;57(4):1974-1981.

4 Finis et al. *Cornea.* 2014;33(12):1265-1270.

5 Blackie et al, Lipiflow Study Group. *Clin Ophthalmol.* 2016;10:1385-1396.

6 Zhao et al. *J Ophthalmol.* 2016;epub 9640643.

7 Toyos R et al. *Photomed Laser Surg.* 2015;33(1):41-46.

8 Craig JP et al. *Invest Ophthalmol Vis Sci.* 2015;56:1965-1970.

9 Rong et al. *Photomed Laser Surg.* 2018;36(10):562-567.

10 Liu et al. *Am J Ophthalmol.* 2017;183:81-90.

11 Arita et al. *Ocul Surf.* 2019;17:104-110.

12 Rong et al. *Photomed Laser Surg.* 2018;36(6):362-332.

Dr. Asbell is Barret G. Haik Endowed Chair of Ophthalmology; director of the Hamilton Eye Institute; and professor of ophthalmology at University of Tennessee Health Science Center in Memphis. *Financial disclosures:* Allergan: C; Bausch + Lomb: C,S; Contact Lens Association of Ophthalmologists: C; MC2: C,S; Medscape: L; Miotech: C,S; NEI: S; Novartis: C,S; Oculus: L; Office of Dietary Supplements-NIH: S; Rtech: C,S; Santen: L; Scientia CME: L; Shire: C; Vindico: L.

Dr. Massaro-Giordano is codirector of the Penn Dry Eye & Ocular Surface Center and professor of clinical ophthalmology at the Scheie Eye Institute at the University of Pennsylvania in Philadelphia. *Financial disclosures:* Celularity: C; GlaxoSmithKline: C; PRN Physician Recommended Nutriceuticals: O.

Dr. Shen is assistant professor of ophthalmology, chair of ophthalmology, and director of the Dry Eye Clinic at the Mayo Clinic in Arizona. *Financial disclosures:* None.

Dr. Tuli is chair and professor of ophthalmology at the University of Florida, Gainesville. *Financial disclosures:* None.

See disclosure key, page 10.



AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet Gives You the Full Picture

Poll-topping, digestible
coverage of all things
ophthalmologic



Visit Us Online
aao.org/eyenet

Write to Us
eyenet@aao.org

Protecting Sight. Empowering Lives.®

Short Term (2 to 8 weeks) Hands on Phaco/S.I.C.S. Surgery Training

At
Dr. P. N. Mahendra Eye Institute
(The Teaching and Training wing of
Khairabad Eye Hospital,
The premier Eye Hospital of Northern India)

Type of Courses offered:
1. For Beginners 2. Advance Course

The Trainee May Perform
60 “HANDS ON” Cases in 4 weeks
Under the Supervision and
guidance of experts.

For Details Contact:
The Administrator,

Dr. P. N. Mahendra Eye Institute
(Khairabad Eye Hospital) Swaroop Nagar, Kanpur
U.P., India Website: www.mahendraeyeinstitute.com
Email:- contact@mahendraeyeinstitute.com
keh01@gmail.com
kehindia@hotmail.com