CEDARS/ASPENS DEBATES

Design of DREAM study raises questions

Alice T. Epitropoulos, MD, FACS, says the study had etiological and methodological variability.

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Alice T. Epitropoulos, MD, FACS

Welcome to another edition of CEDARS/ASPENS Debates. CEDARS/ASPENS is a joint society of cornea, cataract and refractive surgery specialists, here to discuss some of the latest hot topics in ophthalmology.

The use of omega-3 supplements has been a major component of ocular surface management for many eye care professionals. Recently, the authors of the DREAM study proposed that omega-3 use was no better than placebo. This month, **Alice T. Epitropoulos, MD, FACS,** presents her take on this issue and discusses how this data conflicts with her previously published data. We hope you enjoy this discussion.

Kenneth A. Beckman, MD, FACS
OSN CEDARS/ASPENS Debates Editor

Over the last few years we have come to realize the importance of optimizing the surface and its effect on surgical visual outcomes. In fact, dry eye disease is at the root of dissatisfaction or unhappiness with results after refractive cataract surgery. We cannot do premium surgery without a premium tear film.

We published a paper in *Cornea* demonstrating the benefits of taking re-esterified omega-3 supplements for dry eye. This was a multicenter, prospective, interventional, placebo-controlled, double-masked study. Subjects were randomized to receive either 2 g re-esterified omega-3 or a control. We wanted to include only dry eye patients, so we enrolled subjects with stage 1 or 2 meibomian gland dysfunction (MGD) with tear osmolarity of 312 mOsm/L or more on two visits. Subjects were excluded if they used topical cyclosporine, topical corticosteroids or oral omega-3 fatty acids within 3 weeks of screening and any time during the study. We saw a statistically significant reduction in tear osmolarity, our primary endpoint, in the omega-3 group at weeks 6 and 12. There also was a statistically significant improvement in tear breakup time and omega-3 index levels (indicating good absorption), and a significant reduction in Ocular Surface Disease Index (OSDI) symptom scores and MMP-9 positivity.

Alice T. Epitropoulos

I would like to acknowledge Penny Asbell and her co-authors on the work they did in the DREAM study, which was presented recently at this year's American Society of Cataract and Refractive Surgery meeting. This is a real-life NIH-funded clinical trial studying the effects of omega-3 in dry eye patients. Their conclusions stated there was no change in signs or symptoms after 1 year of taking the omega-3 supplements over placebo. There are a few concerns that I have about the design of this study.

All study participants were permitted to use a wide variety of dry eye therapies concurrently and were also permitted to increase, decrease or change the therapies they were on during the study. In fact, 75% of participants in the active group and 78% in the placebo group reported a change in treatment regimen over the course of the study. This makes the entire study somewhat less valid, as the changes in therapies were not consistent. If these were consistent, then at least the study could demonstrate how well omega-3s or olive oil work as a supplement to other treatments, but it certainly does not demonstrate how well they work as a primary treatment. For example, if we add Lumigan (bimatoprost ophthalmic solution 0.01%, Allergan) to Xalatan (latanoprost ophthalmic solution 0.005%, Pfizer), you will likely not see additional effects because the first therapy has already lowered the IOP. That does not mean the second treatment did not work — it just was not additive to the first.

Furthermore, patients with a wide variety of conditions were permitted to participate, including those with systemic diseases such as Sjögren's syndrome, thyroid dysfunction and rheumatoid arthritis. The study did not focus on true dry eye patients as defined by the Tear Film & Ocular Surface Society International Dry Eye Workshop dry eye definition. The consensus definition includes hyperosmolarity, which was not a requirement for the DREAM study; in fact, only 6% of participants had a tear osmolarity greater than 312 mOsm/L in one eye and mild MGD in both eyes.

The study product in the DREAM study was not identified as the re-esterified triglyceride form of omega-3, which is essential for maximal absorption and bioavailability. The study utilized a "fish oil concentrate in the TGC form."

The other concern was the control that was used was not neutral. The control contained 5 g of olive oil, which we know is a natural anti-inflammatory and a large component in the Mediterranean diet well known for its positive health benefits — and it may have dry eye healing properties as well. Regardless, both groups had a statistically significant improvement in OSDI scores over 12 months, contrary to the NIH press release stating, "omega-3 fails to yield beneficial results."

These design flaws introduce significant etiological and methodological variability, creating an uncontrolled study environment in which definitive conclusions cannot be drawn. The results of the DREAM study will not change my recommendations, as I will continue to suggest a re-esterified omega-3 for my dry eye patients.

References:

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For more information:

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Disclosure: Epitropoulos reports she receives grant/research support from Bausch + Lomb, Kala Pharmaceuticals, Ocular Therapeutix, TearLab and PRN; is a consultant/speaker for Alcon, Allergan, AMO, Bausch + Lomb, BlephEx, Omeros, Physician Recommended Nutriceuticals, Shire Pharmaceuticals, Sun, TearLab and TearScience; and has property rights/patent holder for EpiGlare tester.