Title

Effects of Omega-3 Supplementation on Exploratory Outcomes in the Dry Eye Assessment and Management Study

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Authors

Oydanich, Marko
Maguire, Maureen G
Pistilli, Maxwell
et al.

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Reports

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The Dry Eye Assessment and Management (DREAM) Study was a multicenter (27 sites), randomized, double-masked clinical trial for people with moderate to severe dry eye disease (DED).[1] Between October 2014 and July 2016, 535 participants were assigned in a 2:1 ratio to either active omega-3 fatty acid daily supplements (2 g eicosapentaenoic acid and 1 g docosahexaenoic acid) or placebo (5 g refined olive oil). One-year results showed no difference between the omega-3 and placebo groups for the primary outcome of symptoms, as measured by the Ocular Surface Disease Index, or the traditional signs of DED (conjunctival and corneal staining, tear film break-up time, and Schirmer II test results).[1]

Additional signs of DED acquired through use of devices were assessed in the DREAM Study as exploratory outcome measures. Clinical staff completed a certification program including review of the protocol and instructional slides and a written test for each device. Measurements were made according to the manufacturer's instructions.

Testing was performed on both eyes with the right eye first. Tear osmolarity was measured using the TearLab Osmolarity System (TearLab, San Diego, CA). The Keratograph 5M (Oculus, Arlington, WA) was used for noninvasive keratographic tear film break-up time, tear meniscus height, bulbar conjunctival redness, and meibomian gland imaging. The examiner everted each eyelid and used the keratograph's infrared photography system to capture images of meibomian glands. Examiners graded meibomian gland dropout on the Pult scale.[2] When lid eversion or image quality was insufficient to judge dropout area, the result was classified as missing. Matrix metalloproteinase (MMP) 9 testing was performed with the InflammaDry system (RPS Diagnostics, Sarasota, FL). Keratography and tear osmolarity testing was conducted only at centers equipped with the devices. Testing was at baseline, 6 months, and 12 months, except for MMP 9 testing (carried out at screening and 3 months).

Differences between treatment groups were estimated with regression models using a generalized estimating equations approach to account for intereye correlation. Subgroups were defined based on the baseline values of the measures for signs, using category bounds to form tertiles or, for tear osmolarity, a previously defined threshold for abnormal ($\geq$308 mOsm/l). Variation in treatment effects across subgroups was assessed with tests of interaction.

The DREAM Study protocol was approved by each center's institutional review board, complied with the Health Insurance Portability and Accountability Act, and adhered to the tenets of the Declaration of Helsinki. Patients provided written informed consent. The trial was registered on ClinicalTrials.gov (identifier, NCT02128763).

The baseline mean $\pm$ standard deviation value of tear osmolarity in the active group (303.9$\pm$17.2 mOsm/l) was higher than in the placebo group (300.6$\pm$14.5 mOsm/l; $P = 0.02$; Table S1, available at www.aaojournal.org). The mean change was a decrease of 0.7 mOsm/l in the active group and an increase of 3.6 mOsm/l in the placebo group, yielding a difference of 4.3 mOsm/l ($P = 0.02$; Table S2, available at www.aaojournal.org; Fig 1A).

The baseline keratography measurements were similar between treatment groups (Table S1). The mean noninvasive keratographic tear film break-up time decreased by 0.5 second in each group ($P = 0.97$; Table S2; Fig 1B). The change in mean tear meniscus height was near 0 in the active (0.00 mm) and placebo (−0.01 mm) groups ($P = 0.71$; Table S2; Fig 1C). The mean change in bulbar conjunctival redness score was near 0 in the active (0.00) and placebo (−0.01) groups ($P = 0.81$; Table S2; Fig 1D). The percentage of eyes with Pult scale scores indicating improvement, stability, or worsening by 1 or more categories was similar for the upper lid ($P = 0.34$) and lower lid ($P = 0.21$; Table S2).

At baseline, the MMP 9 test showed positive results for similar proportions of eyes in the active (33%) and placebo (30%) groups. Between baseline and 3 months, 10% of eyes in the active group and 13% of eyes in the placebo group converted negative to positive results, and 13% of each group converted from positive to negative results ($P = 0.69$; Table S2).

Results of analyses of the mean difference between active and placebo groups within subgroups are displayed in Table S3 (available at www.aaojournal.org). None of the tests of interaction showed statistically significant results (all $P \geq 0.39$).

In this randomized, double-masked clinical trial, there were no significant differences between daily supplementation with omega-3 versus refined olive oil supplementation in noninvasive keratographic tear film break-up time, tear meniscus height, bulbar conjunctival redness, upper and lower lid meibography, and MMP 9 positivity (all $P > 0.21$). Only the mean change in tear osmolarity yielded a statistically significant difference, with slight improvement in the active treatment group (−0.7 mOsm/l) when compared with the worsening in the placebo treatment group (+3.6 mOsm/l). The mean changes over time within each treatment group were small for keratography measures, and the net change in classification of meibomian gland dropout and MMP 9 positivity was small. When subgroups were examined, there was no evidence of a greater benefit of omega-3 supplementation among eyes with more abnormal values at baseline.

Although a small improvement was observed in the mean change in tear osmolarity for the active group and a worsening in the placebo group, there was no difference between the active and placebo groups at 12 months (303.1$\pm$18.4 mOsm/l vs. 303.3 17.5 mOsm/l; $P = 0.90$). These findings are difficult to interpret given the high variability among readings from the TearLab system and lack of correlation changes in tear osmolarity with changes in symptoms or corneal fluorescein staining.[3,4]