The DREAM Extension Study - Comparison of placebo and omega-3 fatty acid supplement groups on OSDI, 4 key signs of DED and adverse events

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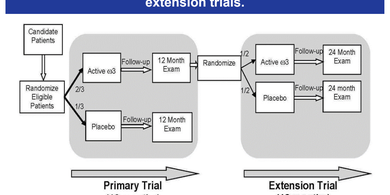
BACKGROUND

- Dry eye disease (DED) is
  - one of the most frequently encountered ocular morbidities.[1]
  - considered one of the top 3 most prevalent chronic eye diseases.
  - Inflammation of the ocular surface is an important component of dry eye disease.[2,3]
- Several clinical trials support role of Omega-3 (ω3) fatty acids in the treatment of DED.[4-7]
  - Outcome measures, dosing, composition, and length of treatment with ω3 vary across these trials.
- The Dry Eye Assessment and Management (DREAM)
  - Primary trial reported no difference between ω3 and placebo supplement groups on symptoms and signs of DED[10]; but symptoms improved in both groups over time.
  - Extension trial aims to study long-term safety and sustainability of any treatment effect and evaluate return of signs and symptoms of DED after withdrawal of ω3 treatment.

PURPOSE

- To determine effects of continued use or discontinuation of ω3 fatty acids among subjects who were assigned to ω3 in the first year of the DREAM primary trial.

Figure 1. Schematic overview of the DREAM primary and extension trials.



METHODS

Trial Design
- Prospective, multi-center, randomized, double-masked clinical trial.

Eligible Subjects
- Assigned to active supplements in the primary trial.
- Completed 12 month study visit in the primary trial.

Treatment
- Randomized 1:1, Active (2000 mg EPA + 1000 mg DHA) : Placebo (5000 mg olive oil).
- Daily for 12 months.

Study Visits
- Enrollment (month 12 of primary trial), months 18 and 24.
- Phone call at months 15 and 21.

Study Procedures
- Ocular Surface Disease Index (OSDI)
- Brief Ocular Discomfort Inventory (BODI)
- Slit lamp evaluation (SLE)
- Evaluation of the Meibomian glands and eyelids
- Lissamine green conjunctival staining
- Corneal fluorescein staining
- Tear break up time (TBUT)
- Schirmer test

Outcome Measures
- Primary: change in dry eye symptoms by OSDI.
- Secondary: changes in clinical signs of DED.

Adverse Events
- Subject reported at each study visit or phone call.
- Coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system.

Statistical Analysis
- Change between 12 and 24 months within treatment groups assessed for linear trend across months 12, 18, and 24.
- Linear regression for comparisons of mean change between treatment groups and associated 95% confidence intervals (CI).
- Chi-square tests for comparisons of categorical outcomes
- Wilson's method for 95% CI's for difference in proportions.

RESULTS

Table 1: Characteristics of active and placebo group at baseline

Characterisitc	Active (N = 22)	Placebo (N = 21)
Age in years, mean	58.2 ±15.0	58.4 ±14.7
Gender, No (%)		
Female	19 (86.4)	17 (81.0)
Male	3 (13.6)	4 (19.0)
Race, No (%)		
White	15 (68.2)	16 (76.2)
Black	2 (9.1)	2 (9.5)
Other	5 (22.7)	3 (14.3)
Ethnicity, No (%)		
Hispanic or Latino	2 (9.1)	0 (0.0)
Other	20 (90.9)	21 (100)
Total OSDI score, mean	27.9 ±19.5	27.8 ±19.6
Short Form -36 score, mean		
Physical health	47.6 ±12.8	48.3 ±9.5
Mental health	51.1 ±10.4	51.4 ±10.0
Brief Ocular Discomfort Index score, mean		
Discomfort subscale	31.7 ±19.4	29.0 ±16.2
Pain interference subscale	16.5 ±21.3	14.9 ±14.1
Dry eye treatments, N (%)		
Artificial tears	13 (59.1)	14 (66.7)
Cyclosporine drops	7 (31.8)	4 (19.0)
Warm lid soaks	4 (18.2)	3 (14.3)
Lid scrubs	3 (13.6)	1 (4.8)
Other	6 (27.3)	7 (33.3)
Systemic disease, N (%)		
Sjogren syndrome	4 (18.2)	2 (9.5)
Thyroid disease	4 (18.2)	2 (9.5)
Rheumatoid arthritis	3 (13.6)	4 (19)
None of the above	14 (63.6)	15 (71.4)
Fatty acid in red blood cells, mean		
Eicosapentaenoic, %	3.0 ±1.0	3.3 ±1.0
Docosahexaenoic, %	6.1 ±0.7	6.2 ±0.7
Oleic, %	10.6 ±1.2	11.4 ±1.4
Conjunctival staining score, mean	2.7 ±1.7	2.1 ±1.7
Corneal staining score, mean	3.3 ±2.9	3.9 ±3.3
Mean Tear break-up time, secs	4.3 ±4.8	3.3 ±2.0
Mean Schirmer test, mm	7.1 ±3.4	7.7 ±5.9

- 22 participants were assigned to the ω3 group and 21 to the placebo group.
- The characteristics of the participants at enrollment were comparable between treatment groups

Figure 2: Ocular Surface Disease Index (OSDI) scores over time

- The mean (±SD) change between month 12 and month 24 in total OSDI score was 3.1±15.1 (p=0.52) in the active group and 3.7±17.8 (p=0.28) in the placebo group.
- The difference in mean change between groups was -0.6 (95% confidence interval CI (-10.7, 9.5); p=0.91)

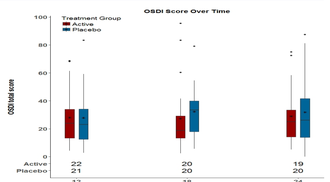
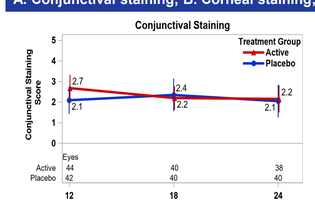
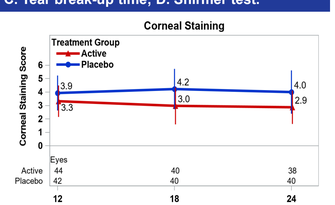


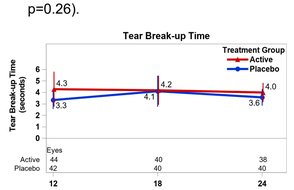
Figure 3: Signs of dry eye disease over time
A. Conjunctival staining; B. Corneal staining; C. Tear break-up time; D. Shirmer test.



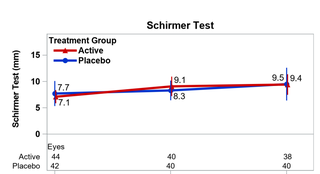
- The mean (±SD) conjunctival staining score decreased in the active group (-0.4±1.0; p=0.04).
- Mean (95% CI) difference in change between groups was -0.4 ((-1.2, 0.3); p=0.26).



- The mean (±SD) corneal staining score decreased in the active group (-0.1±1.7).
- The mean difference in change between groups was -0.3 ((-1.2, 0.7); p=0.60).



- The mean (±SD) TBUT decreased in the active group (-0.6±4.6).
- The mean difference in change between groups was -0.8 secs ((-2.6, 0.9); p=0.35).



- The mean (±SD) Schirmer test increased in both the active (2.4±3.8; p=0.004) and the placebo (1.8±5.4; p=0.03) groups.
- The mean difference was 0.6 mm ((-2.0, 3.2); p=0.65).

CONCLUSIONS

- There was no statistically significant difference in changes in symptoms or signs of DED between patients continuing use of ω3 supplements and patients discontinuing use.
  - Limitation: Small sample size (~20 per group) – low statistical power to detect small or moderate differences.
- Discontinuing the use of ω3 after 12 months may not have significantly inferior outcomes compared to continuing for an additional 12 months.
- Rates of adverse events were similar in both the groups.
- The results from the two DREAM clinical trials together do not support a beneficial effect of ω3 supplementation on dry eye disease.

REFERENCES

1. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clinical ophthalmology (Auckland, NZ). 2009;3:405-12.
2. Wei Y, Asbell PA. The core mechanism of dry eye disease is inflammation. Eye & contact lens. 2014;40(4):248-56.
3. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. The ocular surface. 2017;15(3):438-510.
4. Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. International journal of ophthalmology. 2013;6(6):811-6.
5. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. Ophthalmology. 2017;124(1):43-52.
6. Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, McCulley JP. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. Cornea. 2011;30(3):308-14.
7. Asbell PA, Maguire MG, Pistilli M, Ying GS, Szczotka-Flynn LB, Hardten DR, et al. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. The New England journal of medicine. 2018;378(18):1681-90.

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