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Dry Eye Assessment and Management (DREAM©) Study: Study design and baseline characteristics

Penny A. Asbell[a,*], Maureen G. Maguire[b], Ellen Peskin[b], Vatinee Y. Bunya[b], Eric J. Kuklinski[a], On Behalf of The Dry Eye Assessment and Management (DREAM©) Study Research Group

[a] Icahn School of Medicine at Mount Sinai, Department of Ophthalmology, 1468 Madison Ave, Box 1183, New York, NY 10029, United States
[b] University of Pennsylvania, Department of Ophthalmology, 3535 Market Street, Suite 700, Philadelphia, PA 19104, United States

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ABSTRACT

Purpose: Describe trial design and baseline characteristics of participants in the DRy Eye Assessment and Management (DREAM©) Study.

Design: Prospective, multi-center, randomized, double-masked "real-world" clinical trial assessing efficacy and safety of oral omega-3 (ω3) supplementation for the treatment of dry eye disease (DED).

Methods:

- Setting: Multi-center study (27 sites) consisting of academic and private practices led by ophthalmologists and optometrists throughout the United States.
- Study Population: 535 subjects with symptoms and signs of moderate to severe DED were randomized in a 2:1 ratio to ω3 or placebo. All participants, clinical staff, and laboratory personnel were masked to treatment assignment.
- Intervention: 3000 mg ω3 (2000 mg eicosapentaenoic acid(EPA) and 1000 mg docosahexaenoic acid(DHA)) per day or placebo (5000 mg olive oil per day)
- Primary Outcome: Change in dry eye symptoms (change from baseline to follow-up in the Ocular Surface Disease Index(OSDI) score).

Results: Mean age of participants was 58.0 ± 13.2 years. Mean OSDI score at baseline was 44.4 ± 14.2. Mean conjunctival staining score (scale 0–6) was 3.0 ± 1.4, corneal staining score (scale 0–15) was 3.9 ± 2.7, tear break-up time was 3.1 ± 1.5 s, and Schirmer test was 9.6 ± 6.5 mm/5 min.

Conclusions: DREAM© participants mirror real world patients who seek intervention for their DED-related symptoms despite their current treatments. Results regarding the efficacy of omega-3 supplementation will be helpful to clinicians and patients with moderate to severe DED who are considering omega-3 as a treatment. This trial design may be a model for future RCT's on nutritional supplements and DED treatments seeking to provide useful information for clinical practice.

Trial registration: ClinicalTrials.gov number NCT02128763.

1. Introduction

Dry eye disease (DED) is a multifactorial condition that causes symptoms of ocular discomfort, fatigue, and visual disturbance that interfere with quality of life, and can be described as a chronic pain syndrome [1, 2]. DED affects approximately 14% of adults in the United States [3] and is one of the most common reasons patients seek eye care treatment [4, 5].

The economic burden of DED is significant. The average cost of DED is estimated to be over $59 billion to the US society overall per year, taking into account both healthcare costs and loss of productivity costs [6]. In addition, DED presents an unmet medical need where current treatments are inadequate and expensive. Better treatments are needed that target the underlying pathophysiologic causes of the disease.

Although the pathogenesis of DED is not fully understood, it is recognized that inflammation has a prominent role in its development and chronicity [7, 8]. Regardless of the instigating etiology, DED eventually leads to inflammation of the ocular surface via various mechanisms leading to ocular surface damage and further exacerbation of DED inflammatory processes, thus creating a self-perpetuating vicious cycle of inflammation and DED [8]. Anti-inflammatory therapies may break this cycle of DED and chronic inflammation [9]. Clinicians and

* Corresponding author.
E-mail address: penny.asbell@mssm.edu (P.A. Asbell).

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their DED patients continue to seek better methods to control inflammation and often are particularly attracted to "natural" treatments, such as nutritional supplements like omega-3 fatty acids (ω3).

Clinical trials on the role of poly-unsaturated fatty acids (PUFAs) in various inflammatory diseases have shown anti-inflammatory benefits of supplementation with ω3 PUFAs [10–15]. However, the evidence for the efficacy of ω3 for treating DED is inconsistent, and the studies were of short duration, often had small sample sizes, or were not representative of the general DED population due to restrictive eligibility criteria [9, 16]. Larger, long-term studies with objective measures of compliance are needed to clarify whether or not ω3 supplements are effective and safe for the treatment of DED given that ω3 is normally used on a long term basis. To address this need, the Dry Eye Assessment and Management (DREAM©) Study was carefully designed to provide reliable data on the safety and efficacy of ω3 for the treatment of DED and at the same time improve our understaning of DED. In addition, the methods used in this DED protocol can be applied to other trials to evaluate safety and efficacy of nutritional supplements. Key methodological issues in the protocol design for DREAM© are discussed.

2. Methods

2.1. Overview of trial design

The DREAM© study was a multi-center, double-masked, placebo-controlled, randomized clinical trial (Clinicaltrials.gov Identifier NCT02128763) that provided evidence on the efficacy and safety of ω3 in DED, as well as longitudinal data over one year of observation on a well-defined cohort of typical DED subjects with moderate to severe DED. A one-year course of treatment was selected to diminish the effects of seasonal changes on DED symptom and signs and also to provide safety information on the long-term use of ω3. A total of 535 patients with DED were enrolled across 27 sites throughout the United States. Subjects were randomized in a 2:1 ratio to ω3 (2000 mg eicosapentaenoic acid (EPA), 1000 mg docosahexaenoic acid (DHA) = total 3000 mg ω3 per day) versus placebo (5000 mg olive oil per day) (Fig. 1). Patients were examined at 3, 6 and 12 months. The primary outcome measure was a mean change in symptoms as measured by the Ocular Disease Surface Index (OSDI) from baseline compared to 6 and 12 months. The DREAM© study protocol and informed consent were approved by the respective clinical center institutional review boards or a centralized institutional review board (University of Pennsylvania). The DREAM© study was in compliance with the Health Insurance Portability and Accountability Act, and accepted by the US Food and Drug Administration under an investigational new drug (IND) application (IND 106,387).

2.2. Study treatment

Although various doses have been used in clinical trials to study the role of ω3 supplementation in a variety of diseases [16–30], the dose of 3 g was chosen to achieve a maximal therapeutic effect without added risks, such as bleeding, even when patients were already taking supplements with 1.2 g or less per day of ω3 [31, 32]. A ratio of EPA to DHA of 2:1 was selected because this ratio is found in many natural foods [33, 34], and many studies examining the role of ω3 in DED have used this ratio [16, 17, 35, 36]. Fish oil was chosen over other ω3 sources, such as flaxseed oil, because fish oil is well metabolized in humans and the re-esterified triglyceride form, rather than the ethyl ester form, was chosen because of greater absorption, bioavailability, and stability [37–39]. Participants were instructed to take 5 softgel capsules per day. Each active capsule contained 400 mg EPA and 200 mg DHA, providing a daily dose of 2000 mg EPA and 1000 mg DHA.

Each placebo capsule contained 1000 mg of refined olive oil, which is the most common placebo used in other randomized clinical trials on ω3 supplementation [16, 18, 36, 40–44]. Refined olive oil is much lower in polyphenols as compared to extra virgin olive oil, which is the staple of the Mediterranean Diet. Some studies have shown that polyphenols are the source of the beneficial health effects seen from olive oil [45, 46]. Since the DREAM© placebo is refined olive oil that is low in polyphenols, we did not expect to see an effect on dry eye disease. In addition, the total daily dose of olive oil in DREAM© was 5 g per day, or about 1 teaspoon. Studies testing the benefits of olive oil, usually as part of the Mediterranean Diet, have supplied daily doses of at least 60 g [47], and sometimes as high as 100 g [48], over 20 times higher than the DREAM© placebo. Furthermore, the DREAM© olive oil was 68% oleic acid, an omega-9 fatty acid considered neutral with respect to inflammation. In addition, an objective measurement of systemic fatty acid levels by measuring the levels of fatty acids in erythrocytes (red blood cells) at randomization, 6 and 12 month visits, including oleic acid levels was used to measure how well the fatty acid was

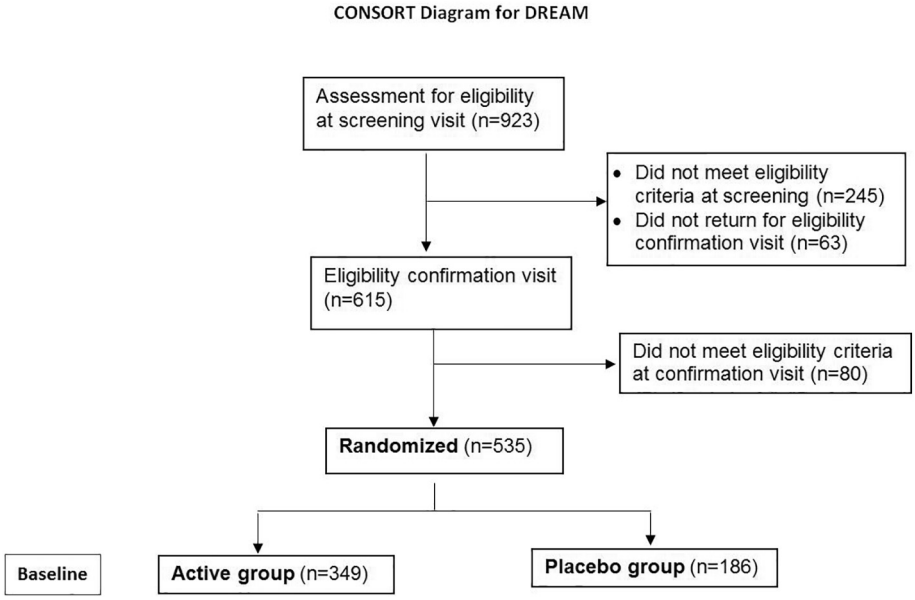

Fig. 1. CONSORT Diagram for the DRy Eye Assessment and Management (DREAM©) Study.