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## Pilot study for treating dry age-related macular degeneration (AMD) with high-dose omega-3 fatty acids

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### ABSTRACT

Age-related macular degeneration (AMD) is the primary cause of blindness in individuals older than 50 years of age. Studies were carried in patients with dry AMD using high-dose omega-3 fatty acids providing 3.4 g of eicosapentaenoic acid (EPA) and 1.6 g of docosahexaenoic acid (DHA) on a daily basis for 6 months. In patients with dry AMD, significant improvement in vision acuity occurred in 100% of patients was observed within four and half months after omega-3 supplementation.

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### 1. Introduction

Age-related macular degeneration (AMD) is the most common cause of severe and irreversible loss of central vision in people over the age of 50. More than 7 million in the U.S. have early to moderate AMD. Severe AMD affects 1.8 million people in the US and the number suffering from AMD is expected to increase by 50% in 2020 [1].

The macula occupies the central section of the retina and is essential for close-up visual information and vital to reading and face recognition. The macula is highly concentrated in photoreceptor cone cells responsible for fine vision. If these are damaged, visual information is no longer adequately relayed to the optic nerve and severe impairment of the central vision is the result. Peripheral vision remains intact, but the quality of life for the patient is significantly reduced to the extent of being considered to be legally blind.

Although the etiology of AMD is unknown, inflammation and oxidative stress appear to play fundamental roles in the pathogenesis of AMD. High sensitivity CRP (hs-CRP) has been used as a marker of systemic low-level chronic inflammation.

Patients with elevated hs-CRP levels (>3 mg/l) had a 31% increased risk of AMD and a nearly 2-fold increased risk of late stages AMD [2]. Complement factor H gene has been identified as the one gene, which significantly increases the risk of AMD by 11 times and the LOC387715 A695 variant increases the risk of AMD by 15 times [3]. These observations suggest that chronic low-grade chronic inflammation may play a role in the development of AMD.

The initial injury in AMD is the retinal pigment endothelium (RPE), which is the layer of cells that lies below the photoreceptors in the macula. This may possibly be due to gene mutation, oxidative stress, light damage, lipofuscin accumulation, complement mediated injury, inflammation or a combination of the above [4]. Regardless of the initiating factors, the result is the formation of cellular debris called drusen that accumulate between the retina and the choroid that contains the blood vessels feeding the retina. The deposition of drusen seems to be involved in the early stages as well as progression of the disease [5].

These observations suggest that local inflammation plays a potentially significant role in the development of AMD [6]. Unfortunately, inflammation remains one of the most complex biological systems. This may be due in part to distinct phases of an acute inflammatory response. First is the classic initiation phase defined by the cardinal signs of inflammation [7,8]. Among the major mediators in this phase of the inflammatory response is the generation of pro-inflammatory eicosanoids generated from the

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omega-6 fatty acid, arachidonic acid (AA). This includes prostaglandins (such as PGE<sub>2</sub>) and leukotrienes (such as LTB<sub>4</sub>). Less appreciated is the resolution phase of inflammation [9–11]. For many years, it was thought that the resolution phase was a consequence of the temporal lessening of the initiation phase similar to the dying out of the embers of burning fire. We now understand that the resolution of inflammation is an active process primarily driven by a new families of mediators termed resolvins derived from the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [12].

Results from animal models have demonstrated the dietary intake of omega-3 fatty acids or a transgenic increase of omega-3 production can substantially reduce the pathological retinal angiogenesis associated with AMD [13]. Since angiogenesis may be a response to inflammation in AMD, the success of omega-3 fatty acid supplementation in animal models would be suggestive that the same may hold for humans. However, two recent clinical trials on dry AMD have provided disappointing results [14,15]. Considering the success in animal studies with omega-3 fatty acid supplementation [13], we undertook an open-label pilot study to investigate the potential that higher doses of omega-3 fatty acids might be required to provide clinical benefits to patients with dry AMD.

## 2. Materials

The Inflammation Research Foundation, Marblehead, MA donated the omega-3 fatty acid concentrates for the study. The omega-3 concentrates consisted of purified ethyl esters rich in EPA (400 mg) and DHA (200 mg) per gram for the liquid formulation. The dosage used in these pilot studies was 10 ml of the liquid formulation providing approximately 3.4 g of EPA and 1.6 g of DHA per day. The dosage was divided into two daily doses of 5 ml each.

Visual acuity was determined by the improvement of lines of vision that could read by a patient using an electronic Early Treatment Diabetic Retinopathy Study (ETDRS) chart during the supplementation period. One line of vision consists of five letters that can be clearly read by the subject. Each line of vision has a geometric progression with increasing difficulty to read.

All subjects who were taking vitamin supplements according to AREDS2 recommendations [16] and were asked to stop this treatment prior to beginning the omega 3 fatty acids supplementation.

## 3. Results

Forty eyes of 25 patients with dry AMD were given the omega-3 fatty acid supplementation (5 g of omega-3 fatty acids consisting of 3.4 g EPA and 1.6 g DHA per day). The mean age was 67 years with a range from 50 years to 85 years. The visual acuity of patients ranged from 20/25 (80% of normal vision) to 20/200 (10% of normal vision) was recorded according to the ETDRS electronic chart. The patients were followed up every 6 weeks for 6 months.

Supplementation with 5 g of omega-3 fatty acids (3.4 g EPA and 1.6 g DHA) per day resulted significant improvement of the average vision in all patients by six months as shown in Fig. 1.

By the six-month time point, the average increase in vision was 2 lines of vision or 10 letters.

All eyes had improvement of visual acuity. Approximately, one-third of eyes improved by 1 line of vision (5 letters), the other third by 2 lines of vision (10 letters) and the last third by 3 lines of vision (15 letters) at the end of 6 months of the omega-3 fatty acids supplementation (Fig. 2).

The time course for improvement of the percentage of subjects with dry AMD that had at least one line of vision (5 letters) improvement is shown in Fig. 3.

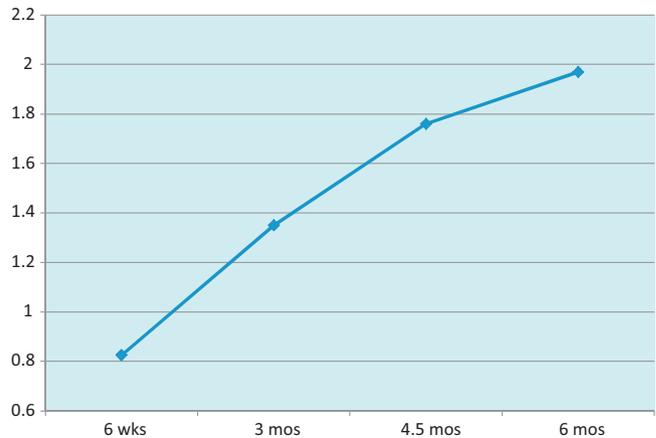


Fig. 1. The average increase in the lines of vision in patients with dry AMD who were being supplemented with omega-3 fatty acids.

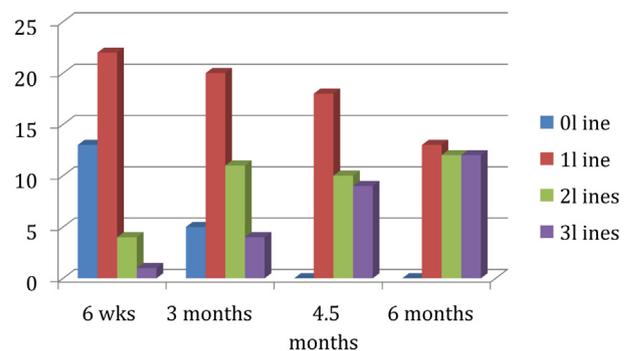


Fig. 2. Gains in lines of vision in dry AMD patients with omega-3 supplementation.

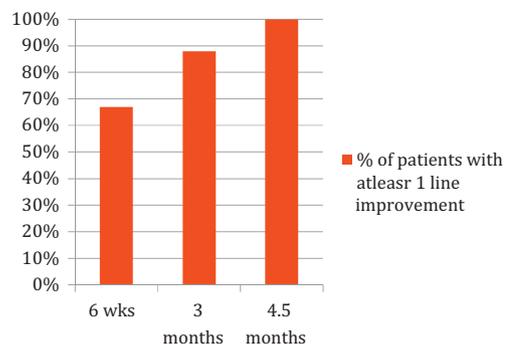


Fig. 3. Time course for improvement of at least one line of vision in patients with dry AMD on omega-3 fatty acid supplementation. The percentage represents the number of patients who had at least one line of vision improvement at each time point.

All patients had gained a minimum 1 line of vision (5 letters) by 4.5 months.

## 4. Discussion

AMD is a growing problem because of an aging population. It is the primary cause of legal blindness in patients greater than 50 years of age. There is no current approved treatment for dry AMD.

Since there is no existing treatment for dry AMD, the positive clinical improvements obtained in this pilot study should be considered striking since 100% of the patients had an increase of at least one line of vision within 4.5 months after starting the

omega-3 fatty acid supplementation. Our results in patients with dry AMD are in stark contrast with recent reports by Gerstenblith et al. [14] who used an omega-3 formulation that was rich in DHA (2.5 g per day), but poor in EPA (0.85 g per day) for a six-month period with negative findings. The AREDS2 Study 2 Research Group used an omega-3 formulation that was low in both EPA (0.65 g per day) and DHA (0.35 g per day) in patients with dry AMD for a five-year period that also gave negative findings [15].

We hypothesize the reason that our open label experiments with high-dose omega-3 fatty acids in the treatment of dry AMD was successful is a consequence of both (a) the increased dosage and (b) the higher levels of EPA delivered with our omega-3 fatty acid formulation. The daily levels of supplemented EPA in our open-label pilot study were 4–5 times greater than the other two negative studies. Our working hypothesis is that resolution of neuroinflammation in the macula may be mediated by E-resolvins derived from the higher daily dose of EPA. Animal studies suggest higher levels of supplementation with omega-3 fatty acids will increase local levels of both precursor EPA and the E-series resolvins in the retina [13].

However, any increased resolvins (E, D, or neuroprotectins) production within the brain requires adequate levels of their precursors in the blood since the brain is incapable of synthesizing long-chain omega-3 fatty acids. It has been demonstrated that rate of entry of the long-chain fatty acids such as arachidonic acid (AA), DHA, and EPA into the brain across the blood-brain barrier are virtually equivalent [17]. This leads to the intriguing question as to why are the levels of EPA so low in the brain compared to other tissues in the body. This paradox appears to be a consequence of EPA becoming rapidly oxidized once it enters into the brain [18,19]. On the other hand, once AA and DHA enter into the brain, they are stored in neural phospholipids that have a very long half-life especially in humans [20]. This difference in metabolism of EPA in the brain compared to DHA may explain the dramatic differences of levels of EPA and DHA in the brain leading to an assumption that EPA has little importance in treating neurological conditions.

Since EPA is an essential fatty acid that has significant anti-inflammatory properties, it initially makes no teleological sense that this particular fatty acid is chosen for rapid oxidation of EPA in the brain while being conserved in other tissues unless its oxidation serves a greater purpose. One possible explanation is that the rapid oxidation of EPA is to maintain adequate levels of anti-inflammatory resolvins in the brain to constantly protect the brain from future inflammatory damage. The rapid enzymatic conversion of EPA in the brain may provide a steady state reservoir of E-series resolvins that may serve as an anti-inflammatory-pro-resolving “insurance policy” against future unexpected inflammatory insults to the brain and the retina. The high doses of EPA used in our supplementation may have supplied adequate levels of EPA to maintain a critical threshold of resolvins of E-series (both RvE1 and RvE2). Since DHA is preferentially stored as phospholipids with a very slow turnover, the metabolism of DHA into resolvins of the D-series or neuroprotectins would be less robust. We speculate that most of the DHA entering into the brain would be stored in the form of phospholipids for long-term storage and therefore not readily available for constant resolvins synthesis. This is also suggested by animal studies in which as the levels of EPA in the brain are significantly increased by dietary supplementation or transgenic manipulation, are correlated with increased levels of E-series resolvins in the blood.

Although the dose of omega-3 fatty acids used in these studies may appear high, in fact the average daily EPA and DHA dose used in the subjects reported was about one-third of those levels used in various prior studies in the treatment of severe brain trauma [21] and ADHD [22,23]. It is also interesting to note that in clinical

studies with patients with bipolar depression, that high-dose omega-3 concentrate (9.6 g per day) containing both EPA and DHA had significant benefits in a placebo-controlled trial [24], whereas using DHA alone had no benefits [25]. The improved therapeutic benefits for EPA compared to DHA also appear to be true for other types of depression as determined by meta-analysis [26]. This would suggest the presence of EPA might be critical for therapeutic benefits in a variety of neurological disorders.

The most common criticism against the use of higher doses of omega-3 fatty acids is that they may potentially lead to increased bleeding. The data to support that contention remain weak [27,28]. Nonetheless, in prior studies with high-dose omega-3 fatty acids [21–23], have used the AA/EPA ratio in the blood as a clinical marker for potential bleeding problems. In those studies, if the AA/EPA ratio dropped below 1, then the omega-3 fatty acid dosage was reduced until the AA/EPA ratio in the blood rose above 1.

In this pilot study, the ability to do fatty acid analysis was not available on site so we have no data on the resulting AA/EPA ratios in the subjects. However, dose-response studies with high-dose omega-3 fatty acids in healthy women at high risk for breast cancer have indicated that up to 7.5 g of EPA and DHA per day for a six-month period reduces the AA/EPA ratio to approximately 1.1 with no adverse side effects reported during study [29]. The AA/EPA ratio reached in this study of healthy American women is similar to that found in the general Japanese population [30]. We assume the subjects in these studies maintained their AA/EPA ratio above the threshold of 1, and thus would not require reducing the omega-3 dose. This assumption is supported by the fact that none of the subjects had any complaints or adverse reactions during the study.

Another indication that bleeding times may not be an issue if one is monitoring the AA/EPA ratio comes from the JELIS study conducted with more than 18,000 subjects using omega-3 fatty acids for the reduction of cardiovascular events [29]. Those in the active group receiving the additional omega-3 concentrates reduced their AA/EPA ratio in the plasma from 1.6 to 0.8 over a 3.5-year period. At the conclusion of the study, those with the lowered AA/EPA ratio had 20% fewer cardiovascular events than the control group although both groups were taking statin drugs. However, those in the active group did have a slightly increased number of bleeding events compared to the control group. Therefore at this time, we believe that maintaining an AA/EPA ratio in the blood greater than 1 provides an adequate safety factor to minimize any concerns about extensive bleeding while at the same time providing a clinical marker indicating whether or not the patient is obtaining a therapeutic dosage of EPA and DHA.

In conclusion, this open label pilot study suggests that omega-3 fatty acid supplementation, rich in EPA, may aid the resolution of inflammation in the macula and thus improving the vision in patients with dry AMD. The vision improvement in the subjects with dry AMD is significant and uniform. Since there is no currently approved treatment for dry AMD, high-dose omega-3 fatty acid supplementation may represent a significant therapeutic option for such patients.

The limitations of these preliminary studies are (a) the limited number of subjects studied, (b) the lack of a placebo-controlled treatment group, and (c) the absence of measurement of the AA/EPA ratio, (d) the lack of measurement of levels of resolvins (both E and D series) in the blood, and (e) the lack of measurement of isoprostanes in the blood to demonstrate that there is little, if any, increased oxidative stress induced by the high-dose omega-3 fatty acid supplementation. All these parameters need to be correlated with the improvement of the vision to support our working hypothesis of the potential mode of action. Additional clinical trials to address these limitations of this pilot study are currently in progress.

## Layperson's summary

This open-label pilot study suggests high-dose omega-3 fatty acids may be effective in treating age-related macular degeneration, which is the leading cause of blindness over the age of 50.

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