PharmaNutrition 2 (2014) 8–11

Contents lists available at ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu

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

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ARTICLE INFO

Article history:
Received 29 August 2013
Received in revised form 7 October 2013
Accepted 9 October 2013

Keywords:
Age-related macular degeneration
Omega-3 fatty acids
Resolvins
Eicosapentaenoic acid
Inflammation
Clinical treatment

Chemical compounds studied in this article:
Eicosapentaenoic acid (EPA)
docosahexaenoic acid (DHA)

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 3.4g of eicosapentaenoic acid (EPA) and 1.6g 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.

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 (>3mg/l) had a 31% increased risk of AMD and a nearly 2-fold increased risk of late stages AMD [2]. Compliment 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 omega-6 fatty acid, arachidonic acid (AA). This includes prostaglandins (such as PGE_2) and leukotrienes (such as LTB_4). 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

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2213-4344/$ - see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.phanu.2013.10.001

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 transgenetic 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 (400mg) and DHA (200mg) per gram for the liquid formulation. The dosage used in these pilot studies was 10ml of the liquid formulation providing approximately 3.4g of EPA and 1.6g of DHA per day. The dosage was divided into two daily doses of 5ml 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 (5g of omega-3 fatty acids consisting of 3.4g EPA and 1.6g 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 5g of omega-3 fatty acids (3.4g EPA and 1.6g 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.

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.

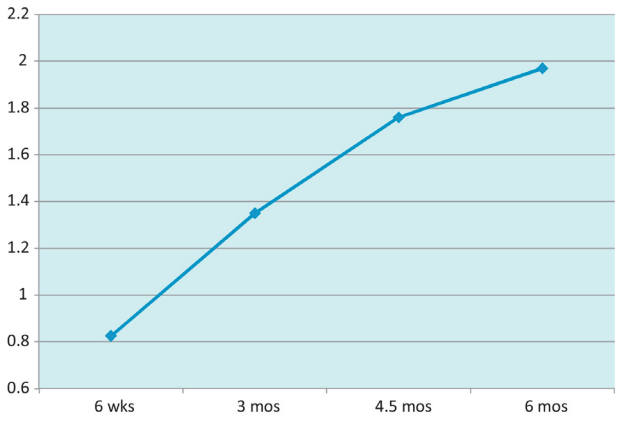

Fig. 1. The average increase in the lines of vision in patents with dry AMD who were being supplemented with omega-3 fatty acids.

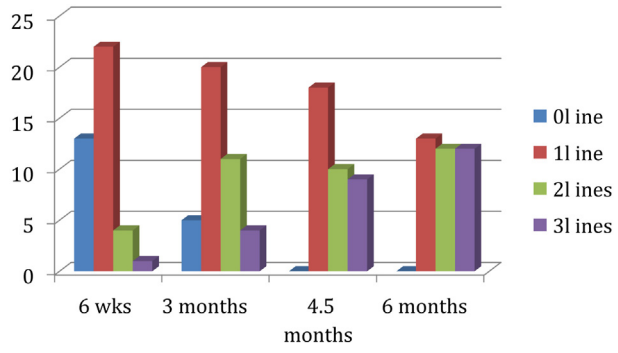

Fig. 2. Gains in lines of vision in dry AMD patients with omega-3 supplementation.

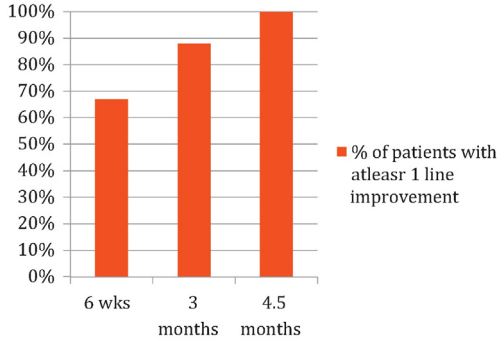

Fig. 3. Time course for improvement of at least one line of vision in patients with dry AMD on omega-3 fatty acid supplementation. The percentage represents the number of patients who had at least one line of vision improvement at each time point.

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 (2.5g per day), but poor in EPA (0.85g 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 (0.65g per day) and DHA (0.35g per day) in patients with dry AMD for a five-year period that also gave negative findings [15].