Four-Year Placebo-Controlled Trial of Docosahexaenoic Acid in X-Linked Retinitis Pigmentosa (DHAX Trial)

A Randomized Clinical Trial

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IMPORTANCE X-linked retinitis pigmentosa is a severe inherited retinal degenerative disease with a frequency of 1 in 100,000 persons. Because no cure is available for this orphan disease and treatment options are limited, slowing of disease progression would be a meaningful outcome.

OBJECTIVE To determine whether high-dose docosahexaenoic acid (DHA), an ω-3 polyunsaturated fatty acid, slows progression of X-linked retinitis pigmentosa measured by cone electroretinography (ERG).

DESIGN, SETTING, AND PARTICIPANTS A 4-year, single-site, randomized, placebo-controlled, double-masked phase 2 clinical trial at a research center specializing in medical retina. Seventy-eight male patients diagnosed as having X-linked retinitis pigmentosa were randomized to DHA or placebo. Data were omitted for 2 patients with non-X-linked retinitis pigmentosa and 16 patients who were unable to follow protocol during the first year. The remaining participants were tested annually and composed a modified intent-to-treat cohort (DHA group, n = 33; placebo group, n = 27).

INTERVENTIONS All participants received a multivitamin and were randomly assigned to oral DHA (30 mg/kg/d) or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of loss of cone ERG function. Secondary outcomes were rod and maximal ERG amplitudes and cone ERG implicit times. Capsule counts and red blood cell DHA levels were assessed to monitor adherence.

RESULTS Average (6-month to 4-year) red blood cell DHA levels were 4-fold higher in the DHA group than in the placebo group (P < .001). There was no difference between the DHA and placebo groups in the rate of cone ERG functional loss (0.028 vs 0.022 log μV/y, respectively; P = .30). No group differences were evident for change in rod ERG (P = .27), maximal ERG (P = .65), or cone implicit time (no change over 4 years). The rate of cone loss (ie, event rate) was markedly reduced compared with rates in previous studies. No severe treatment-emergent adverse events were found.

CONCLUSIONS AND RELEVANCE Long-term DHA supplementation was not effective in slowing the loss of cone or rod ERG function associated with X-linked retinitis pigmentosa. Participant dropout and lower-than-expected disease event rate limited power to detect statistical significance. A larger sample size, longer trial, and attainment of a target blood DHA level (13%) would be desirable. While DHA supplementation at 30 mg/kg/d does not present serious adverse effects, routine monitoring of gastrointestinal tolerance is prudent.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00100230

Published online May 7, 2014.

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X-linked retinitis pigmentosa (XLRP) is an orphan retinal degenerative disease with a frequency in the population of approximately 1 in 100 000,1,2 resulting in about 3000 affected individuals in the United States. The clinical characteristics of XLRP include diminished visual acuity, progressive night blindness in early childhood due to loss of rod photoreceptor function, tunnel vision attributable to loss of cone and rod function beginning in the second or third decade of life, and concomitant appearance of retinal pigmentation in the fundus. Subsequent disease progression results in legal blindness. Although the disease has genetic origins, a persistent confounding observation is that many families with a history of retinitis pigmentosa display variations in disease severity and/or onset of symptoms despite having the same gene mutation.3-4 This inconsistency may be multifactorial and encompass additional genetic modifiers as well as environmental factors such as diet that may contribute to the dysfunctions in visual processing.

Of particular significance to retinal function in XLRP is the ω-3 fatty acid docosahexaenoic acid (DHA; 22:6 ω-3), found highly enriched in cold-water fish. In humans, DHA is the most unsaturated fatty acid present in biological membranes and accounts for 1% to 5% of total fatty acids in many tissues. However, DHA accounts for 30% to 40% of fatty acids in phospholipids of the retina and is concentrated in the outer segments of rod and cone photoreceptors.5 It is found tightly associated with rhodopsin in rod outer segments,6 influences membrane fluidity and permeability,7 promotes photoreceptor differentiation,8 has antiapoptotic activity,9 and influences expression of genes associated with neurogenesis and apoptosis.10 The DHA derivative neuroprotectin 1 has neuroprotective properties including scavenging of free radicals and promoting retinal cell survival.9 Thus, optimizing the microenvironment of photoreceptor membranes may be beneficial in slowing progression in retinal degenerative diseases.

Reduced blood levels of DHA are found in many males with XLRP.11,12 Because measurement of retinal DHA in relatively healthy individuals with XLRP is unattainable, we infer that the correlation (r = 0.82) of retinal DHA with red blood cell (RBC) DHA found in nonhuman primates13 permits the use of RBCs as a surrogate index for retinal tissue levels. When adjusted for age, patients with XLRP with the lowest RBC DHA content tend to have lower rod (r = 0.57; P = .009)14 and cone (r = 0.81; P = .001)15 electroretinography (ERG) amplitudes. Substantive evidence that DHA is incorporated into the retina comes from studies in which infants given formulas enriched with DHA have improved retinal maturation compared with infants receiving little or no DHA in their diet.16

There is no cure for retinitis pigmentosa (including XLRP) and treatment options are limited. Vitamin A supplementation (15 000 IU/d) has a modest effect on the rate of cone ERG progression.16 In patients taking vitamin A, supplementation with 1200 mg of DHA per day showed no benefit over placebo on peripheral visual fields, cone ERG function, or visual acuity.17 However, a post hoc analysis on a subset of patients who had not previously taken vitamin A suggested that the combination of vitamin A and DHA led to significant preservation of visual field sensitivity compared with vitamin A only.18

In a 4-year, placebo-controlled, randomized clinical trial, participants (ages 4-38 years) received 400 mg/d of DHA or placebo; however, owing to large variations in body weight, the dosage of DHA varied from 3 to 23 mg/kg/d.19 Supplementation with DHA increased the mean RBC DHA level from 2.7% to 6.9% and was associated with an average 25% reduction in the rate of cone ERG decline vs placebo (P = .12). An inverse correlation between blood DHA levels and loss of cone ERG function (r = −0.38; P = .01) suggested that an RBC DHA level of approximately 13% should minimize cone ERG loss. To attain this level, a DHA dosage of approximately 30 mg/kg/d is needed. Adverse events associated with this long-term DHA regimen were minimal20; however, this low dosage of DHA reduced plasma vitamin E levels by 15%, suggesting that the highly unsaturated nature of DHA may impede antioxidant potential. Thus, in the present study (Docosahexaenoic Acid in X-Linked Retinitis Pigmentosa [DHAX] trial), a minimal antioxidant status was maintained in all participants by provision of a basic multivitamin.

The objectives of the 4-year, placebo-controlled, randomized clinical DHAX trial were to use oral DHA supplementation in an attempt to increase RBC DHA levels to approximately 13% and to determine whether this level of supplementation slows the yearly loss of cone ERG function in patients with XLRP.

Methods

Study Population

The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center, Dallas. Eligible patients and/or parents of minors provided written informed consent. The use of DHA in this trial with minors was conducted under an Investigational New Drug approval from the US Food and Drug Administration. Study oversight was provided by a data and safety monitoring committee.

Male patients clinically diagnosed as having XLRP were recruited from the Southwest Eye Registry in Dallas, the Foundation Fighting Blindness database, and referrals from US and Canadian ophthalmologists. Telephone interviews or e-mails were exchanged with 216 relatives or individuals with retinal diseases. Medical and visual function records were reviewed for 128 patients, and 90 were invited to Dallas for evaluation (Figure 1). Participants (ages 7-31 years) meeting entry criteria were assigned to DHA (n = 41) or placebo (n = 37) using a computer-generated randomization schedule with varying block sizes. To maintain XLRP homogeneity, data were omitted for 2 participants determined to have mutations in genes not associated with XLRP. Sixteen participants were unable to follow protocol during the first year (eAppendix in Supplement). The remaining 60 participants were tested annually and composed a modified intent-to-treat (mITT) cohort (placebo, n = 27; DHA, n = 33). Participants who completed the trial and adhered to the protocol throughout it composed a prespecified per protocol cohort (placebo, n = 22; DHA, n = 29). Enrollment commenced August 5, 2005, and ended June 1, 2008; all
The modified intent-to-treat (mITT) cohort (n = 60) included data for trial participants completing at least the first-year annual visit. The per protocol cohort (n = 51) included participants following protocol and completing the 4-year trial. DHA indicates docosahexaenoic acid; XLRP, X-linked retinitis pigmentosa.

8 Dropouts after year 1 annual visit

2 Completed trial but removed because genetically did not have XLRP

5 Dropouts after year 1

29 Completed 4-y per protocol

Clinical Evaluation
Clinical tests conducted annually included the primary outcome of cone ERG amplitudes to 31-Hz flicker stimuli and secondary ERG outcomes of rod and maximal ERG amplitudes and cone ERG implicit times. Blood DHA level and anthropometric measurements (ie, body weight, height, and body mass index) are also reported herein.

ERG Assessment
Full-field ERGs were obtained with a bipolar contact lens electrode and an Espion2 system using achromatic flashes and standards established by the International Society for Clinical Electrophysiology of Vision.21 The fundamental harmonic derived from fast Fourier transform22 spectral analysis of computer-averaged, light-adapted cone ERG amplitude to a 31-Hz flicker was the primary outcome measure. Cone b-wave implicit time was derived from the time between a test flash and corresponding b-wave peak. Rod amplitudes and maximal (mixed cone-rod) amplitudes were elicited from the dark-adapted eye.

Fatty Acid Analysis
Fatty acids in RBCs were analyzed by gas chromatography according to previously detailed procedures.23 Results are presented as relative weight percentage.

Treatment-Emergent Adverse Events
Participants self-reported health-related issues and treatment-emergent adverse events (TEAEs) at annual visits and in quarterly diaries. Serious TEAEs were to be reported immediately (n = 0). Blood chemistry results were monitored annually for TEAEs according to the Division of AIDS criteria.24

Gene Mutation Analysis
Knowledge of XLRP gene mutations was not an entry criteria; thus, screening of participants was conducted during the course of the trial as an ancillary measure by colleagues at the Human Genetics Center, University of Texas Health Science Center, Houston, and at the University of Michigan Kellogg Eye Center, Ann Arbor. Methods for mutation analysis have been described.25,26

Sample Size Determination
The estimated mean (SE) rate of decline in cone ERG function in XLRP in the absence of treatment (ie, event rate) was 0.065 (0.007) log μV/y.19 Assuming a treatment effect of 40%, statistical significance for a 2-sided test using a significance level of .05 and 80% power would require 24 participants per group.27

Statistical Analysis
Data from all patients with XLRP completing at least 1 year of the trial were used in the mITT cohort analysis (n = 60). On trial termination, there was a preliminary analysis of data integrity and data lock followed by repeated-measures mixed-model regression analysis. Statistical significance was set at P < .05.
Results

Baseline Characteristics
Patients who received DHA supplementation were slightly older than patients in the placebo group (mean, 16.1 vs 14.9 years, respectively) and had marginally higher RBC DHA levels (Table 1). All other demographic and anthropometric measures were similar between groups.

RBC DHA Levels
For participants in the mITT DHA group, the mean (SE) RBC DHA level increased 3.3-fold from a baseline level of 3.12% (0.15%) to 10.10% (0.52%) by trial year 4 (P < .001) (Figure 2). At a 30-mg/kg/ddosage, RBC DHA levels reached a plateau within the first 6 months. For participants in the placebo group, RBC DHA levels at baseline and year 4 were 2.85% and 2.82%, respectively (P = .82), indicating that participants did not modify their dietary behavior. Overall, the 6-month to 4-year average increase in the RBC DHA level was 4-fold higher in the DHA group than in the placebo group (mean [SE], 10.89% [0.32%] vs 2.71% [0.13%], respectively; P < .001). The mean (SE) adherence to protocol based on capsule count monitoring was 84.6% (3.4%) for the placebo group and 89.4% (1.9%) for the DHA group (P = .19).

Primary Outcome Measure
A main effect of time was identified for light-adapted cone 31-Hz ERG amplitudes (P < .001), with the XLRP population showing significant progression. A main effect of DHA treatment assignment was not identified (P = .30) (Table 2) and no interaction between assignment group and year was evident (P = .62).

Secondary ERG Functions
No difference between the placebo and DHA groups was evident for the rates of rod or maximal ERG functional loss.

Table 1. Baseline Demographic Characteristics of Modified Intent-to-Treat Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 27)</th>
<th>DHA (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other and mixed</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hispanic ethnicity, No.</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Vitamin A intake &gt;7500 IU/d from years 0 to 4, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minors*</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Adults</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Age, mean (SE) [range], y</td>
<td>14.9 (1.1) [7-28]</td>
<td>16.1 (1.4) [7-31]</td>
</tr>
<tr>
<td>&lt;18 y, No.</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>≥18 y, No.</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Weight, mean (SE) [range], kg</td>
<td>62 (6) [22-123]</td>
<td>58 (5) [23-116]</td>
</tr>
<tr>
<td>Weight for age in minors only, mean (SE) [range], %a</td>
<td>65 (6) [20-98]b</td>
<td>67 (5) [30-98]b</td>
</tr>
<tr>
<td>Height, mean (SE) [range], cm</td>
<td>161 (4) [122-194]</td>
<td>159 (4) [122-191]</td>
</tr>
<tr>
<td>BMI, mean (SE) [range]</td>
<td>23 (1) [15-39]</td>
<td>22 (1) [15-34]</td>
</tr>
<tr>
<td>RBC DHA, mean (SE) [range], %d</td>
<td>2.86 (0.10) [1.8-3.8]</td>
<td>3.12 (0.15) [1.8-6.3]</td>
</tr>
<tr>
<td>Mutations, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPGR</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>RP2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Unidentified</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHA, docosahexaenoic acid; RBC, red blood cell.

a Minors are considered individuals younger than 18 years.
b Sample size was 20.
c Sample size was 21.
d The mean (SE) RBC DHA normative value (in 29 age-matched individuals) was 2.91% (0.15%).
e In a protocol deviation, 1 participant volunteered to limit his fish intake if enrolled in the trial.
in the mITT cohort (\(P = .27\) and .65, respectively) (Table 2).

Similarly, cone ERG flicker implicit time demonstrated no differences with assignment group or time (Table 2).

### Table 2. Baseline Characteristics and Yearly Rates of Change in ERG Outcome Measures for Modified Intent-to-Treat Cohort

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Placebo (n = 27)</th>
<th>DHA (n = 33)</th>
<th>Yearly Rate of Change</th>
<th>P Value for Effect of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundamental harmonic of FFT LA 31-Hz cone ERG amplitude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log μV, mean (SE) [range]</td>
<td>0.693 (0.084) [−0.32 to 1.33]</td>
<td>0.761 (0.083) [−0.51 to 1.53]</td>
<td>−0.022 (0.002)</td>
<td>.30</td>
</tr>
<tr>
<td>μV, mean (SE)</td>
<td>7.1 (1.2)</td>
<td>10.5 (1.2)</td>
<td>−0.95 (1.00)</td>
<td>.62</td>
</tr>
<tr>
<td>Annual % loss</td>
<td>4.9</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rod ERG amplitude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log μV, mean (SE) [range]</td>
<td>0.828 (0.080) [0.500 to 2.012]</td>
<td>0.813 (0.082) [0.477 to 2.105]</td>
<td>−0.023 (0.001)</td>
<td>.27</td>
</tr>
<tr>
<td>μV, mean (SE)</td>
<td>6.73 (1.20)</td>
<td>6.50 (1.21)</td>
<td>−0.95 (1.00)</td>
<td>.77</td>
</tr>
<tr>
<td>Annual % loss</td>
<td>6.0</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximal ERG amplitude</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log μV, mean (SE) [range]</td>
<td>1.253 (0.094) [0.362 to 2.359]</td>
<td>1.300 (0.089) [0.491 to 2.359]</td>
<td>−0.036 (0.001)</td>
<td>.65</td>
</tr>
<tr>
<td>μV, mean (SE)</td>
<td>17.8 (1.2)</td>
<td>20.0 (1.2)</td>
<td>−0.92 (1.00)</td>
<td>.77</td>
</tr>
<tr>
<td>Annual % loss</td>
<td>8.0</td>
<td>9.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cone ERG implicit time, mean (SE) [range], ms</td>
<td>38.7 (0.9) [25 to 46]</td>
<td>38.9 (0.7) [30 to 46]</td>
<td>0.12 (0.02) [no change over 4 y]</td>
<td>.77</td>
</tr>
</tbody>
</table>

### Figure 3. Fast Fourier Transform (FFT) Cone Electroretinography (ERG) 31-Hz Amplitudes as a Function of Time for Participants in the Modified Intent-to-Treat Cohort

Mean log μV values for each trial year in participants receiving placebo or docosahexaenoic acid (DHA) supplementation. For placebo vs DHA groups, \(P = .58\) at year 1; \(P = .34\) at year 2; \(P = .21\) at year 3; and \(P = .34\) at year 4. The lower limit of normal FFT cone amplitudes is 1.43 log μV (27.0 μV). Error bars indicate standard error.

* There was a 14% event rate for the placebo group in the phase 1 X-linked retinitis pigmentosa clinical trial.

** There was an 18% event rate for patients with X-linked retinitis pigmentosa in the natural history study.

### Supplemental Vitamin A Intake

Four participants in the placebo group and 5 in the DHA group had a daily intake of 7500 to 15 000 IU of vitamin A throughout the 4-year trial (Table 1). Not surprisingly with these small numbers, the rates of change in cone ERG amplitude and secondary ERG outcomes were similar to participants taking vitamin A or not in both the placebo group (\(P > .12\)) and the DHA group (\(P > .12\)).

### Associations Between ERG Function and RBC DHA Level

No association was evident between the rate of change in cone ERG amplitude and RBC DHA level (Pearson correlation \(r = 0.19\); \(P = .18\)). The RBC DHA level was not correlated with rod and maximal ERG amplitudes or cone implicit times (\(P > .10\)).

### Per Protocol Analysis

Participants in the DHA group of the per protocol cohort (n = 29) had a mean (SE) 6-month to 4-year RBC DHA level of 11.1% (0.2%) (range, 8.9%-13.9%). The distribution of average RBC DHA levels among these participants was as follows: 8.0% to 9.9% DHA, n = 5; 10.0% to 10.9% DHA, n = 9; 11.0% to 11.9% DHA, n = 7; 12.0% to 12.9% DHA, n = 7; and 13.0% to 13.9% DHA, n = 1. The level of DHA in RBCs of the placebo groups for the per protocol and mITT cohorts were identical. Mixed-model analysis of the annual rates of change in cone, rod, or maximal ERG amplitudes or cone ERG implicit times in the per protocol cohort did not demonstrate DHA vs placebo group differences or show marked variation from those in the mITT cohort (data not shown).
Genetic Homogeneity
Mutations in **RPGR** were found in 25 participants (93%) in the placebo group and 29 participants (88%) in the DHA group (Table 1). The frequencies of **RPGR** and **RP2** in our population are in agreement with published literature. No DHA treatment effect was found for cone ERG flicker responses for only participants with mutations in **RPGR** \((P = .19)\).

Treatment-Emergent Adverse Events
Of 78 enrolled participants, 51 had no TEAEs. Twenty-seven participants had a total of 42 related or possibly related TEAEs (22 in the DHA group and 20 in the placebo group). Self-reported and blood chemistry TEAEs were sporadic with no identifiable trends; the exception was 1 participant with a family history of Crohn disease who was sensitive to DHA supplementation. No severe TEAEs requiring hospitalization were reported in the 4-year trial interval. Further details addressing safety and metabolism in the DHAX trial are available (D.K.H.-W., D.G.B., G.E.F., R.S., N.S.P., A.T., D.R.H., unpublished data, August 2005 to May 2012).

Discussion
No effect was found on the annual rate of decline in the primary outcome measure, cone ERG amplitude, by 30 mg/kg/d of DHA supplementation during the 4-year DHAX trial \((P = .30)\) despite greater than a 3-fold elevation in the RBC DHA level. The annual rate of loss of cone ERG function, the event rate, in this cohort of participants was lower than that found in previous studies demonstrating the superiority of a placebo-control trial design over a historical-control trial design. In a 4-year natural history study, the loss of cone ERG function in patients with XLRP averaged 0.085 log μV/y (18% loss per year). In a 4-year phase 1 clinical trial, cone ERG amplitude in the placebo group decreased by 0.065 log μV/y (14% loss per year). In the present trial, the event rate in the mITT placebo group was only 0.022 log μV/y (4.9% loss per year) (Table 2). Participants receiving DHA had a rate of cone loss of 0.028 log μV/y (6.2% loss per year), which by comparison with previous studies would have represented a marked reduction in ERG functional loss. Similarly, the event rate for rod ERG function was reduced in the current trial. In our phase 1 trial, participants in the placebo arm lost 0.079 log μV/y (16.6% loss per year) compared with a loss of 0.023 log μV/y (6.0% loss per year) in the DHAX trial. It is not clear why the event rates in the placebo group were lower than in previous studies. It was not due to the use of fast Fourier transform to derive the fundamental frequency, since the time-domain measure of 31-Hz amplitude similarly declined \((0.024 \log \mu V/y)\). Systematic changes in equipment are unlikely to be the cause since calibrations were performed monthly. Genetic makeup may affect the rate of progression because a retrospective analysis in patients with **RPGR** mutations reported a mean rate of decline of 7.1% for cone ERG amplitude. Age of participants with XLRP is unlikely to be responsible because the age range is similar to that in previous studies. It seems unlikely that ingredients in the corn/soy oil placebo influenced the event rate. However, all participants received a multivitamin to support systemic antioxidant levels; this supplement may have slowed the rate of loss relative to previous studies. It is also possible that improvements in general health and awareness of diet during the past 20 years have influenced the rate of progression.

Trial participants receiving DHA at a dosage of 30 mg/kg/d had an average 4-fold elevation in the RBC DHA level compared with those receiving placebo. For a single participant, the highest average RBC DHA level was 13.9%. The target of 30 mg/kg/d falls within the range of DHA that infants receive in breast milk. Worldwide, breastfeeding provides between 3 and 84 mg/kg/d of DHA depending on maternal diet. In other studies, the mean (SE) RBC DHA level increased over 6 months from 2.8% (0.1%) to 11.1% (0.3%) in children with cystic fibrosis who received DHA supplementation at a dosage of 50 mg/kg/d; the RBC DHA level in 2 patients reached 13.1%. In children with peroxisomal diseases receiving DHA at a dosage of 100 mg/kg/d, the mean (SE) plasma DHA level increased 5-fold in 1 year from 5.3 (2.7) μg/mL to 26.3 (7.4) μg/mL. It remains uncertain whether a maximum ceiling for blood DHA level was attained in the DHAX trial or in recent DHA supplementation trials. No correlations were found between RBC DHA level and rates of ERG decline.

In previous trials in hereditary retinal disease, 14 children with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency receiving DHA at a dosage of 65 to 130 mg/d for at least 2 years had moderate benefits in visual acuity and retinal function as measured by visual evoked potentials and ERG, respectively. Children with peroxisomal disorders \((n = 23)\) receiving DHA at a dosage of 200 mg/d had improvements in nystagmus, visual acuity, and ERG function. In a placebo-controlled randomized trial of patients with peroxisomal disorders receiving placebo \((n = 11)\) or DHA at a dosage of 100 mg/kg/d \((n = 8)\) for 1 year, no group differences in ERG function were found. In 20 patients with Stargardt macular degeneration receiving DHA at a dosage of 840 mg/d for 6 months, no improvements in visual acuity or multifocal ERG amplitudes were found. In a crossover study of DHA at a dosage of 20 mg/kg/d, 8 patients with Best macular dystrophy had 2- to 3-fold elevations in plasma DHA level and improvements in multifocal ERGs.

In a phase 1 trial in which patients with XLRP received DHA at a dosage of 400 mg/d, biochemical safety was not compromised by supplementation for 4 years. Similarly, adults with retinitis pigmentosa receiving DHA at a dosage of 1200 mg/d for 4 years displayed no adverse effects. The occurrence of TEAEs in the DHAX trial was consistent with these safety outcomes, although it would be prudent to closely monitor patients choosing to take high doses of DHA, particularly those prone to or with a family history of gastrointestinal problems.

The strengths of the DHAX trial include genetic homogeneity, use of a single study site, a long intervention period, RBC DHA monitoring of compliance, and close adherence to protocol. A lower-than-expected event rate and an underpowered trial due to participant dropout were primary trial limitations. A larger sample size, longer trial, and attainment of target blood DHA levels of 13% would have been desirable.
Conclusions

Elevated DHA levels did not effectively slow disease progression as measured by cone and rod ERG function. However, the event rate for this trial was unexpectedly less than predicted from previous studies in XLRP. Although there is a strong rationale for DHA supplementation, the DHAX trial along with previous trials using ω-3 fatty acids have yet to demonstrate compelling evidence of efficacy.

REFERENCES


Kayser-Fleischer Ring and Sunflower Cataract in Wilson Disease

Jagat Ram, MS; Amit Gupta, MS

A. Slitlamp biomicroscopy revealed the Kayser-Fleischer ring in the peripheral cornea of a 10-year-old child with Wilson disease. B. A dilated pupillary examination of the lens demonstrated classic sunflower cataract.