Further Evaluation of Docosahexaenoic Acid in Patients With Retinitis Pigmentosa Receiving Vitamin A Treatment

Subgroup Analyses

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Objective: To determine whether docosahexaenoic acid will slow the course of retinal degeneration in subgroups of patients with retinitis pigmentosa who are receiving vitamin A.

Design: A cohort of 208 patients with retinitis pigmentosa, aged 18 to 55 years, were randomly assigned to 1200 mg of docosahexaenoic acid plus 15000 IU/d of vitamin A given as retinyl palmitate (DHA+A group) or control fatty acid plus 15000 IU/d of vitamin A (control+A group) and followed up over 4 years. Seventy percent of the patients in each group were taking vitamin A, 15000 IU/d, prior to entry. We compared rates of decline in ocular function in the DHA+A vs control+A groups among the subgroups defined by use or nonuse of vitamin A prior to entry. We also determined whether decline in ocular function was related to red blood cell phosphatidylethanolamine docosahexaenoic acid level, dietary ω-3 fatty acid intake, or duration of vitamin A use. Main outcome measures were Humphrey Field Analyzer visual field sensitivity, 30-Hz electroretinogram amplitude, and visual acuity.

Results: Among patients not taking vitamin A prior to entry, those in the DHA+A group had a slower decline in field sensitivity and electroretinogram amplitude than those in the control+A group over the first 2 years (P=.01 and P=.03, respectively); these differences were not observed in years 3 and 4 of follow-up or among patients taking vitamin A prior to entry. In the entire cohort, red blood cell phosphatidylethanolamine docosahexaenoic acid level was inversely related to rate of decline in total field sensitivity over 4 years (test for trend, P=.05). This was particularly evident over the first 2 years among those not on vitamin A prior to entry (test for trend, P=.003). In the entire control+A group, dietary ω-3 fatty acid intake was inversely related to loss of total field sensitivity over 4 years (intake, <0.20 vs ≥0.20 g/d; P=.02). The duration of vitamin A supplementation prior to entry was inversely related to rate of decline in electroretinogram amplitude (P=.008).

Conclusions: For patients with retinitis pigmentosa beginning vitamin A therapy, addition of docosahexaenoic acid, 1200 mg/d, slowed the course of disease for 2 years. Among patients on vitamin A for at least 2 years, a diet rich in ω-3 fatty acids (≥0.20 g/d) slowed the decline in visual field sensitivity.

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We have reported elsewhere in this issue that oral supplementation with docosahexaenoic acid in a dosage of 1200 mg/d did not, on average, slow the rate of decline in ocular function over a 4-year interval among 208 patients with retinitis pigmentosa who concurrently received vitamin A, 15000 IU/d. Among these patients randomly assigned to docosahexaenoic acid plus vitamin A (DHA+A group) or control fatty acid capsules plus vitamin A (control+A group), about 70% reported taking vitamin A, 15000 IU/d, prior to entry, whereas 30% did not; approximately equal numbers of patients on and not on vitamin A prior to entry were in the DHA+A and control+A groups. After 1 year of follow-up, we unexpectedly noted a highly significant statistical interaction between the effect of docosahexaenoic acid supplementation and the status of vitamin A intake prior to entry on change in visual field sensitivity (P<.01), suggesting the need for subgroup analyses. Therefore, we followed change in ocular function in these 4 subgroups over the 3 remaining years of this trial. The present article compares rates of decline in ocular function over 4 years among the subgroups within the
DHA + A and control + A groups defined by use or non-use of vitamin A prior to entry.

Data from our previous clinical trial of vitamin A for retinitis pigmentosa showed that the decline in 30-Hz electroretinogram (ERG) amplitude over a 4-year interval was inversely related to red blood cell phosphatidylethanolamine docosahexaenoic acid (RBC PE DHA) concentration (P = .03) among 61 patients for whom we had RBC levels available for analysis at year 3 or 4.1 Because RBC DHA levels have been correlated with retinal DHA levels,2 and DHA concentration is high in the PE fraction of retinal phospholipids,3 we evaluated the relationship of rate of loss of ocular function to RBC PE DHA levels in the present study population. Because RBC phospholipids vary with manipulation of dietary ω-3 fatty acids,4,5 we also evaluated in the control + A group alone whether rate of decline in ocular function could be related to dietary ω-3 fatty acid intake as a measure of docosahexaenoic acid intake.

In our previous trial of vitamin A supplementation for retinitis pigmentosa, we found a significantly slower rate of decline in retinal function in those patients randomized to 15000 IU/d of vitamin A than in those not on this dosage, but this difference became obvious only after 4 years of follow-up.4 In the present study, we therefore also evaluated whether the rate of decline in ocular function in the control + A group was related to duration of vitamin A intake prior to entry.

## METHODS

Patients with retinitis pigmentosa, aged 18 to 55 years, underwent screening for eligibility according to ocular, dietary, and medical criteria and were randomly assigned to a DHA + A or a control + A group. All eligible patients had typical forms of retinitis pigmentosa with elevated final dark-adaptation thresholds, retinal arteriolar narrowing, and reduced and delayed ERGs; most had intraretinal bone spicule pigment around the midperipheral fundus. Atypical forms such as paravenous, unilateral, or sector retinitis pigmentosa were excluded. Patients with Bardet-Biedl syndrome, Refsum disease, retinitis punctata albescens, or retinitis pigmentosa associated with profound congenital deafness were also excluded. Patients were subdivided according to whether or not they reported taking 15000 IU/d of vitamin A prior to entry. Study design, eligibility criteria, informed consent, techniques for evaluation, main outcome measures, method of randomization, procedures for masking, and methods of data analyses are described elsewhere.3 Within 6 to 8 weeks after a screening examination, eligible patients were randomly assigned to a baseline examination to 600 mg of oral docosahexaenoic acid twice daily (DHA + A group) or control fatty acid capsules (control + A group). All were given 1 tablet per day containing 15000 IU of vitamin A as retinyl palmitate. The study was approved by the institutional review boards of the Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, Mass. The study conforms to the Declaration of Helsinki.

Subgroup analyses are listed as follows. First, rates of decline in ocular function were compared between the DHA + A and control + A groups among the subgroups taking vitamin A prior to entry and between the DHA + A and control + A groups among the subgroups not taking vitamin A prior to entry over the 4-year study.

Second, analyses were performed relating rate of decline in ocular function to category of RBC PE DHA level based on an equal-interval scale of percentage of total RBC PE fatty acids (<5.0%, 5.0%-9.9%, 10.0%-14.9%, and 15.0%-19.9%) in the entire study population and in the 2 subgroups defined by vitamin A status prior to entry.

Third, in the entire control + A group (ie, those receiving control fatty acids plus 15000 IU/d of vitamin A regardless of vitamin A status prior to entry), analyses were performed relating rates of decline in ocular function to level of dietary ω-3 fatty acid intake (at or above and below the median intake of 0.20 g/d observed over the course of this study) over the 4-year period of this study and for the periods years 0 to 2 and 2 to 4.

Fourth, in the entire control + A group, we subdivided patients on the basis of duration of vitamin A intake (15000 IU/d prior to study entry (ie, not on vitamin A prior to entry, on vitamin A prior to entry for 1-23 months, or on vitamin A prior to entry for ≥24 months) and compared rates of decline in ocular function among these subgroups.

In addition, in the entire control + A group, we evaluated whether a relationship existed between dietary ω-3 fatty acid intake and RBC PE DHA levels and whether vitamin A intake was associated with a change in RBC PE DHA levels over the duration of the study.

## RESULTS

### Table 1

| Table 1 | gives demographic and ocular characteristics at baseline for the 208 patients seen annually for all 4 years in the DHA + A vs control + A groups within the subgroups defined by status of vitamin A intake prior to entry. In accord with the criteria for randomization, the subgroups defined by vitamin A status prior to entry had no significant differences in percentages of patients by genetic type of retinitis pigmentosa and no significant differences in dietary intake of ω-3 fatty acids at baseline. The study population was about 50% male and 50% female, with a comparable distribution in the subgroups on or not on vitamin A prior to entry. Eleven percent reported partial hearing loss, with no significant difference among the subgroups.

Baseline ocular function (ie, mean of screening and baseline examinations prior to treatment) showed slightly less visual field sensitivity in the DHA + A vs control + A groups within the subgroups, although the differences were not statistically significant in either subgroup. Visual acuity according to the Early Treatment Diabetic Retinopathy Study (ETDRS acuity) and ERG amplitudes at baseline were also not significantly different between the DHA + A and control + A groups in either subgroup (Table 1). Within the subgroups defined by vitamin A use prior to entry, the DHA + A and control + A groups showed comparable levels of RBC PE DHA, plasma DHA, serum retinol, and serum retinyl esters prior to treatment. The RBC PE DHA levels (expressed as the mean ± SE percentage of total RBC PE fatty acids) were significantly higher among those on vitamin A (4.66% ± 0.13%) vs those not on vitamin A prior to entry (4.22% ± 0.16%) (P = .05).

For those on vitamin A prior to entry, RBC PE DHA levels at follow-up were 13.12% ± 0.26% (n = 73) in the DHA + A group and 5.02% ± 0.21% (n = 66) in the control + A group. For those not on vitamin A prior to entry, RBC PE DHA levels at follow-up were 11.98% ± 0.68% (n = 29) in the DHA + A group and 4.31% ± 0.25% (n = 34) in the control + A group. These RBC levels were consistent with
Patients received either 1200 mg/d of docosahexaenoic acid plus 15 000 IU/d of vitamin A (DHA + A) or control capsules plus 15 000 IU/d of vitamin A (control + A). *Unless otherwise indicated, data are expressed as mean ± SE (number of patients sampled). Patients received either 1200 mg/d of docosahexaenoic acid plus 15 000 IU/d of vitamin A (DHA + A) or control capsules plus 15 000 IU/d of vitamin A (control + A). **Interaction of DHA + A versus control + A was significant (P = .002) for 0.5-Hz ERG, loge 10.57 ± 0.32 (1308) 12.99 ± 8.05йдет 9.23 ± 8.05 (1057) .00.002

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reported compliance, ie, 90% of patients reported taking the study capsules 90% of the time.

**ANALYSES OF OUTCOME MEASURES**

**Effect of Docosahexaenoic Acid Supplementation as a Function of Vitamin A Status Prior to Entry**

Table 2 lists mean annual rates of decline of central and total visual field sensitivity, 30-Hz ERG amplitude, and ETDRS acuity over a 4-year interval among the 208 patients in the DHA+A vs control+A groups for those on and not on vitamin A prior to entry. We found significant statistical interactions of treatment effects according to vitamin A supplement use prior to entry for visual field sensitivity and 30-Hz ERG amplitude, suggesting that treatment group effects were different for those on vs not on vitamin A prior to entry. For those on vitamin A prior to entry, the mean annual rates of decline of central and total field sensitivity and 30-Hz ERG amplitude were not significantly different between the DHA+A and control+A groups. For those not on vitamin A prior to entry, mean rates of decline of central and total visual field sensitivity and 30-Hz ERG amplitude were significantly lower in the DHA+A vs control+A groups. No significant statistical interaction effect was noted for ETDRS acuity, and no significant differences in rates of ETDRS acuity decline were noted in subgroup comparisons.

Figure 1A shows values (mean ± SE) of total visual field sensitivity (total point score for Humphrey Field Analyzer [HFA] 30-2 and 30/60-1 programs combined) by year among those not on vitamin A prior to entry in the DHA+A vs control+A groups. In these subgroups, the difference between the 2 curves was larger during years 1 and 2 and smaller during years 3 and 4. In contrast, as seen in Figure 1B, among those on vitamin A prior to entry, the differences between the curves for the DHA+A vs control+A groups were not significantly different for either time period, although a slight divergence of the curves was noted particularly in years 3 and 4. Figure 1C shows the annual rates (mean ± SE) among those not on vitamin A prior to entry for years 0 to 2 and 2 to 4 for rate of total field sensitivity decline when comparing the DHA+A vs control+A groups. The rate of decline was significantly slower in the DHA+A vs control+A groups for years 0 to 2 (P = .006), but was not significantly different for years 2 to 4 (P = .57).

**Relationship of Change in Ocular Function to RBC PE DHA Level**

Table 3 summarizes that, for the entire study cohort, a trend toward a significantly faster decline in visual field sensitivity was seen for those with lower compared with higher RBC PE DHA levels over 4 years (central field test for trend, P = .09; total field test for trend, P = .05). Patients with an RBC PE DHA level of less than 5% of total RBC PE fatty acids showed a significantly faster rate of loss of total field sensitivity vs those with a level of at least 5% (P = .02). Among those not on vitamin A prior to entry, a significantly faster decline was seen for those with lower compared with higher RBC PE DHA levels from years 0 to 2 (central field test for trend, P = .01; total field test for trend, P = .003). These significant differences were not seen from years 2 to 4, although the trends were in the same direction as from years 0 to 2. Among those on vitamin A prior to entry, no significant differences in rate of loss of central or total HFA sensitivity by RBC PE DHA level were seen for years 0 to 2 or years 2 to 4 (Table 3).

**Effect of Dietary ω-3 Fatty Acid Intake on Change in Ocular Function**

Table 4 shows that among patients in the control+A group on vitamin A prior to entry, the rate of decline in visual field sensitivity over a 4-year interval for the central (30-2) condition was significantly related to the amount of dietary ω-3 fatty acid intake; those with an intake of at least 5%...
0.20 g/d had a 40% to 50% slower rate of decline compared with those with intake of less than 0.20 g/d ($P = .02$). A similar result was seen for the total (HFA 30-2 and 30/60-1 combined) condition ($P = .05$). Similar trends were seen for years 0 to 2 and 2 to 4, although the differences were not significant for the latter period ($P = .03$). The same pattern was seen for the 30-2 and total conditions among those not on vitamin A prior to entry, but the differences were not significant (data not shown).

**Effect of Duration of Vitamin A Intake on Change in Ocular Function**

**Table 5** lists data for patients in the entire control + A group categorized by the number of years on vitamin A, 15,000 IU/d, prior to entry. Although their initial 30-Hz ERG amplitudes did not differ significantly, those on vitamin A for 2 or more years prior to entry had the slowest rate of decline during the study, whereas those not on vitamin A prior to entry had the fastest rate of decline. Estimated annual rates of decline of remaining retinal function were 13.0% for those not on vitamin A prior to entry, 11.6% for those on vitamin A for 1 to 23 months prior to entry, and 7.9% for those on vitamin A for 2 or more months prior to entry. There was a significant linear trend with duration of intake of vitamin A prior to entry (test for trend, $P = .008$). A similar trend was seen for central field and total field sensitivity decline. With respect to total field sensitivity, patients in the control + A group showed an 84-dB annual decline during the study for those not on vitamin A prior to entry, a 42-dB decline during the study for those taking vitamin A for 1 to 23 months prior to entry, and a 62-dB decline for those taking vitamin A for 2 or more years prior to entry (test for trend, $P = .08$).

**OTHER ANALYSES**

**Relationship of ω-3 Fatty Acid Intake to RBC PE DHA Levels**

**Figure 2** shows that a significant relationship existed between dietary ω-3 fatty acid intake and RBC PE DHA...
level for the patients in the control + A group (P < .001). The analysis shows that a 0.20-g/d dietary intake of ω-3 fatty acids corresponds to an RBC PE DHA level of approximately 5%.

Association Between Vitamin A Intake and RBC PE DHA Levels

In the control + A group (ie, those receiving control fatty acids plus vitamin A, 15 000 IU/d), irrespective of vitamin A status prior to entry, mean RBC PE DHA level increased significantly from 4.27% (weighted average of 4.39% and 4.04%; Table 1) at baseline to 4.78% at year 4 (mean ± SE increase, 0.51% ± 0.11%; P < .001). Although intake of dietary ω-3 fatty acids increased from 0.18 to 0.26 g/d in the control + A group, a significant rise from baseline in RBC PE DHA remained after adjusting for change in intake of dietary ω-3 fatty acids as measured by the average intake of dietary ω-3 fatty acids for all follow-up visits minus the intake of dietary ω-3 fatty acids at baseline (P = .001).

The present study shows that among patients with retinitis pigmentosa not previously taking vitamin A, those who receive a new supplementation of a combination of docosahexaenoic acid plus vitamin A have a significantly slower rate of decline in visual field sensitivity and 30-Hz ERG amplitude than those given vitamin A alone for 2 years. For this 2-year period, among those not already taking vitamin A prior to entry, those given docosahexaenoic acid along with vitamin A lost, on average, 25 dB of sensitivity, whereas those given vitamin A alone lost, on average, 141 dB. Considering their total visual field sensitivity at baseline (Table 1) and the amount of decline over the first 2 years (Figure 1A), the DHA + A group lost, on average, 2% (25 dB/1276 dB), whereas the control + A group lost, on average, 10% (ie, 141 dB/1436 dB); the saving was, therefore, about 8% over 2 years. This beneficial effect did not persist beyond year 2. For those already taking 15 000 IU/d of vitamin A prior to the onset of the trial, docosahexaenoic acid supplementation did not provide additional benefit.

Among the entire study population, those with lower RBC PE DHA levels (< 5% of total RBC PE fatty acids) had a significantly faster rate of decline in visual field sensitivity than those with higher RBC PE DHA levels over...
Similarly, a significant inverse relationship has been shown by others between rate of loss of cone ERG amplitude over 4 years and RBC DHA level among patients with X-linked retinitis pigmentosa. It has been proposed that a concentration gradient of DHA normally exists in the subretinal space between the rod outer segments (higher concentration) and the retinal pigment epithelium (lower concentration) and that the release of 11-cis retinal from interphotoreceptor retinoid-binding protein (IRBP) is facilitated when IRBP is exposed to sufficient DHA in the subretinal space (Figure 3). It is known that the DHA concentration is reduced in the outer retina in canine and murine models of hereditary retinal degeneration. Whether degeneration leads to loss of DHA or vice versa is not established, but a lack of DHA may impair release of 11-cis retinal (ie, the active form of vitamin A) that is essential for photoreceptor survival. Because the RBC DHA level is thought to reflect the retinal level of DHA, we propose that an RBC PE DHA fatty acid level less than 5% may indicate that the subretinal level of DHA is insufficient to release 11-cis retinal from IRBP.

![Figure 3](https://example.com/figure3.png)

Figure 3. Model for interphotoreceptor retinoid-binding protein (IRBP)-mediated targeting of retinoids to their sites of action in the eye. The model is based on the following 3 observations: (1) docosahexaenoic acid (DHA) is enriched in photoreceptor rather than retinal pigment epithelium (RPE); (2) this fatty acid constitutes a large fraction of fatty acids bound to IRBP endogenously; and (3) the addition of docosahexaenoic acid switches IRBP retinoid-binding site 2 from a state in which it possesses a high affinity for 11-cis retinal (RAL) to a state in which it is incapable of binding this ligand. It is proposed that when IRBP is localized near RPE, its fatty acid–binding site is occupied with fatty acids that are enriched in these cells, such as palmitate. Under these conditions, IRBP adopts a conformation (shaded) that confers a high affinity for RAL on retinoid-binding site 2 (bottom left corner of this scheme). When IRBP moves across the interphotoreceptor matrix (IPM) to the vicinity of the photoreceptors, its fatty acid content is readjusted according to the fatty acids prevalent in these cells to contain a large fraction of DHA. Binding of DHA switches the protein to a conformation (unshaded) in which site 2 has a very low affinity for RAL, resulting in rapid release of this ligand. Site 2 then becomes occupied with all-trans-retinol (ROL), the affinity for which remains high in the presence of DHA. The process is reversed when IRBP moves back to the proximity of RPE. The overall outcomes of the cycle are that RAL moves to photoreceptors, ROL is transported to RPE, and the fatty acids transfer down their concentration gradients. (The affinity of IRBP’s retinoid-binding site 1 for ROL and RAL is only marginally affected by fatty acids. This site may function simply as a buffer that nonspecifically allows for elevated concentrations of retinoids in the IPM.) ROS indicates rod outer segment. Reprinted with permission from Wolf.10 Used with permission from the International Life Sciences Institute, Washington, DC.
this regard, the control+A group (ie, patients receiving control fatty acids plus vitamin A) showed a significant rise in their RBC PE DHA level during the course of the study that was independent of change in dietary ω-3 fatty acid intake. This may partially explain why the treatment effect of docosahexaenoic acid was significant in the first 2 years of the study only among those who were not taking vitamin A prior to entry. Those taking vitamin A prior to entry may have already elevated their RBC PE DHA level sufficiently to modify the course of their disease. Indeed, the mean level of RBC PE DHA was significantly higher among patients on vs those not on vitamin A prior to entry.

A significant relationship was also observed between the level of dietary ω-3 fatty acid intake and the rates of decline of central and total field sensitivity among patients in the control+A group on vitamin A prior to entry (Table 4). A level of dietary intake of ω-3 fatty acids of at least 0.20 g/d, which corresponds to an RBC PE DHA level of about 5% or greater (Figure 2), was associated with a slower rate of decline in visual field sensitivity than a level of intake of less than 0.20 g/d. These findings support the hypothesis that patients with retinitis pigmentosa taking vitamin A would benefit from maintaining an average dietary intake of ω-3 fatty acids of at least 0.20 g/d. This is equivalent to one to two 84-to-112-g (3- to 4-ounce) servings per week of fish rich in ω-3 fatty acids, such as salmon, tuna, mackerel, sardines, or herring.\(^{15}\)

The clinical significance of an average dietary intake of ω-3 fatty acids of at least 0.20 g/d among patients with retinitis pigmentosa who receive vitamin A supplements can only be estimated. If the rates of decline of central visual field sensitivity observed during this study persist long-term, and if the average central field sensitivity of a patient aged 37 years is about 869 dB (Table 1, control+A group on vitamin A prior to entry), we propose that an average patient on vitamin A who maintains an intake of ω-3 fatty acids of 0.20 g/d after 37 years of age would be expected to lose about 21 dB per year (Table 4) and, therefore, would lose virtually all central field sensitivity by 78 years of age (ie, [869/21] +37). In contrast, an average patient receiving vitamin A with dietary intake of ω-3 fatty acids of less than 0.20 g/d after 37 years of age would be expected to lose 39 dB per year (Table 4) and would lose virtually all central field sensitivity by 59 years of age (ie, [869/39] +37). Therefore, maintenance of a dietary intake of ω-3 fatty acids of at least 0.20 g/d after 37 years of age could result in an estimated 19 years of additional vision for the average patient with retinitis pigmentosa who combines vitamin A, 15000 IU/d, with a diet rich in ω-3 fatty acids.

In a previous trial of vitamin A for retinitis pigmentosa, we reported that those receiving vitamin A palmitate, 15000 IU/d, showed an 8.3% annual rate of decline in remaining 30-Hz ERG amplitude over 6 years compared with a 10.0% annual decline among those in the trace control group receiving vitamin A at a dosage of 75 IU/d.\(^{6}\) The beneficial effect of 15000 IU/d of vitamin A was best seen after patients had received this dosage for several years.\(^{6}\) In the present 4-year study, patients on 15000 IU/d of vitamin A for 2 or more years prior to entry showed a significantly smaller loss of remaining 30-Hz ERG amplitude per year (7.9%) compared with those not on vitamin A prior to entry (13%) or on vitamin A for less than 2 years (11.6%) (Table 5). A similar trend was seen for visual field results. These data suggest that, in the absence of docosahexaenoic acid supplementation, at least 2 years are required before the beneficial effect of vitamin A on the course of retinitis pigmentosa is fully achieved.

Together the results show that docosahexaenoic acid supplementation shortens the interval for vitamin A to take its full effect and supports a recommendation that most adult patients with the typical forms of retinitis pigmentosa who start vitamin A therapy at a dosage of 15000 IU/d should also take docosahexaenoic acid, 1200 mg/d for 2 years (600 mg twice a day). No evidence was found of a continued benefit of docosahexaenoic acid supplementation beyond the first 2 years, leading to the recommendation that patients receiving vitamin A should stop docosahexaenoic acid supplementation after 2 years. A slight tendency toward adversity was noted in years 3 and 4 among patients on vitamin A, 15000 IU/d, prior to entry in the DHA+A group (Figure 1B), further supporting discontinuation of docosahexaenoic acid therapy at a dosage of 1200 mg/d after 2 years.

It must be emphasized that these conclusions are based on group averages, and, therefore, no assurance can be given that a specific patient will benefit from this treatment. This study did not include patients younger than 18 years or those receiving a dosage of less than 1200 mg/d of docosahexaenoic acid, and therefore no formal recommendation can be made for younger patients or for a smaller dosage. The study also did not include patients with central visual field sensitivity in the HFA of less than 250 dB with a size V test light or patients with best-corrected visual acuity of less than 20/100 in both eyes, and therefore no formal recommendation can be made for such patients. Because patients were advised to stop docosahexaenoic acid and vitamin A therapy during pregnancy and because of the increased risk of birth defects among patients receiving high-dose vitamin A supplementation,\(^{10}\) patients who are pregnant or planning to become pregnant should not take this combination of supplements.

In addition, these data suggest that adult patients with retinitis pigmentosa who have taken 15000 IU/d of vitamin A for at least 2 years should eat 1 to 2 servings of fish rich in ω-3 fatty acids weekly (equivalent to an average food intake of ω-3 fatty acids of at least 0.20 g/d) to maintain an RBC PE DHA level of at least 5% of total RBC PE fatty acids. A test to determine RBC PE DHA level is not widely available. As an alternative, physicians should consider obtaining a fasting RBC DHA level about 3 months (ie, considering RBC turnover) after patients start eating ω-3-rich fish and periodically thereafter. We have observed a high correlation between RBC PE DHA and RBC DHA levels in patients with retinitis pigmentosa not on docosahexaenoic acid supplementation (r=0.96, n=49); an RBC DHA level of 4% of RBC total lipid fatty acids will ensure with 95% confidence that the RBC PE DHA level is at least 5% in a given patient (E.L.B., B.R., M.A.S., C.W.-D., and A.M., unpublished data, 2004).
The present study also supports a previous recommendation that most adults with the typical forms of retinitis pigmentosa should continue to take 15,000 IU/d of vitamin A palmitate under medical supervision to slow the course of their condition. It should be noted that the precursor of vitamin A, betacarotene, is not predictably converted into vitamin A; therefore, betacarotene is not a suitable substitute for vitamin A palmitate in the context of this treatment regimen.

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