Follow-up of 89 Asymptomatic Patients With Adrenoleukodystrophy Treated With Lorenzo’s Oil

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Objectives: To identify asymptomatic boys with X-linked adrenoleukodystrophy who have a normal magnetic resonance image (MRI), and to assess the effect of 4:1 glyceryl trioleate–glyceryl trierucate (Lorenzo’s oil) on disease progression.

Method: Eighty-nine boys (mean ± SD baseline age, 4.7 ± 4.1 years; range, 0.2-15 years) were identified by a plasma very long-chain fatty acids assay used to screen at-risk boys. All were treated with Lorenzo’s oil and moderate fat restriction. Plasma fatty acids and clinical status were followed for 6.9 ± 2.7 years. Changes in plasma hexacosanoic acid levels were assessed by measuring the length-adjusted area under the curve, and a proportional hazards model was used to evaluate association with the development of abnormal MRI results and neurological abnormalities.

Results: Of the 89 boys, 24% developed MRI abnormalities and 11% developed both neurological and MRI abnormalities. Abnormalities occurred only in the 64 patients who were aged 7 years or younger at the time therapy was started. There was significant association between the development of MRI abnormalities and a plasma hexacosanoic acid increase. (For a 0.1-µg/mL increase in the length-adjusted area under the curve for the hexacosanoic acid level, the hazard ratio for incident MRI abnormalities in the whole group was 1.36; \( P = .01 \); 95% confidence interval, 1.07-1.72.) Results for patients aged 7 years or younger were similar (\( P = .04 \)).

Conclusions: In this single-arm study, hexacosanoic acid reduction by Lorenzo’s oil was associated with reduced risk of developing MRI abnormalities. We recommend Lorenzo’s oil therapy in asymptomatic boys with X-linked adrenoleukodystrophy who have normal brain MRI results.

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with ALD and examine whether administration of 4:1 glyceryl trioleate–glyceryl trierucate (Lorenzo’s oil [LO]) to asymptomatic patients with ALD can reduce the risk of developing neurological abnormalities.

Dietary therapy intended to reduce the levels of VLCFA was introduced in 1981. A diet that sharply reduced the intake of saturated VLCFA did not alter plasma C26:0 levels. This suggested that dietary intake is not the main source of the VLCFA that accumulates in ALD and led to attempts to reduce endogenous synthesis. In 1986, it was demonstrated that the addition of monounsaturated oleic acid reduced the levels and the rate of synthesis of saturated VLCFA in cultured skin fibroblasts of patients with ALD and that oral administration of glyceryl trioleate for a period of 3 to 4 months lowered plasma C26:0 levels by approximately 50%. In 1989, one of the authors (A.O.) pioneered the concept of erucic acid therapy for patients with ALD on the basis of a review of lipid manipulation in animal studies and reports that erucic acid and saturated long-chain fatty acid are elongated by the same microsomal enzyme systems. This led to the production of LO, which was shown to normalize the levels of saturated VLCFA within 4 weeks in most patients with ALD. The striking effect of LO on plasma C26:0 levels engendered the hope that it would be of clinical benefit for patients with ALD. However, a series of single-arm clinical trials led to the consensus that the oil did not alter the rate of progression significantly in patients who were already neurologically symptomatic when therapy was initiated. In the absence of a placebo-controlled study, a definitive conclusion is not possible.

The present study aims to determine whether LO has a preventive effect. Because of the devastating nature of CERALD, combined with the hope that the striking reduction of plasma VLCFA levels would lead to clinical benefit, it was practically impossible and ethically questionable to conduct a placebo-controlled study. (We are currently planning such a study in those with the AMN phenotype; they have a less severe disease course and hence do not pose an ethical challenge.) We therefore developed an alternative evaluation criterion at the outset of the study, namely the association between the reduction of plasma VLCFA levels and clinical outcome. Reduction of plasma VLCFA levels, particularly levels of C26:0, is the principal biochemical effect of LO. In this study, we examine the hypothesis that there is an association between the decrease in C26:0 levels and 2 measures of clinical outcome, namely the time to development of neurological and MRI abnormalities in patients with ALD in whom the therapy was initiated when their neurological examination and brain MRI results were normal. A preliminary report from our group, in a study of shorter duration, suggested that such an association exists.

In summary, our main objectives were (1) to understand the nature and progression of the disease course in asymptomatic boys with ALD who have normal brain MRI results and (2) to assess whether the lowering of plasma VLCFA levels by LO in asymptomatic patients delays the development of MRI and neurological abnormalities.
levels. There were no instances of abnormal bleeding or other adverse events.

OUTCOME MEASURES

Neurological examination and brain MRI studies were scheduled at 6- to 12-month intervals and were used to define outcomes. For the neurological assessment, we used the 25-point scale devised specifically for ALD.26 The MRI results were ported separately. Brain MRI results were assessed with the 34-tient was classified as neurologically abnormal if he received a score of 2 or higher. Neuropsychological function will be reported separately. Brain MRI results were assessed with the 34-point scale devised specifically for ALD.26 The MRI results were classified as abnormal if the score was 1 or higher. In both cases, a binary outcome was defined by classifying a patient as normal or abnormal. Once a diagnosis of abnormality was made, no patient experienced disease remission.

ASSOCIATION BETWEEN C26:0 LEVELS AND OUTCOME MEASURE

The Cox proportional hazards regression model in SAS/STAT PROC PHREG27 was used to analyze the relationship between C26:0 levels and the time from study entry to disease progression. No additional covariates were used in the proportional hazards model. Adjustment for age at entry was done by stratifying at baseline age (cutoff was at age 7 years, as boys younger than age 7 years at entry represented the high-risk population for developing MRI or neurological abnormalities).

Separate “survival” analyses were conducted for the time to radiological and neurological progression; the former always preceded the latter. The C26:0 levels were analyzed as a time-dependent covariate (TDC) with various functions of the repeated C26:0 values explored as possible predictors of progression. This method requires that, at the time a progression is observed for any child (ie, at the elapsed years since study entry), the value of the TDC must be evaluated for each child in follow-up who had not already progressed. Alternative forms explored for the TDC were the time-weighted average since study entry (length-adjusted area under the curve [LAUC] equal to the area under the curve divided by follow-up time), the most recent value of C26:0, the value 1 year before the present time, and the average and largest values in the most recent year (all set to “missing” if there was no observation in the year). Where appropriate, linear interpolation was used to estimate the TDC value at the time of each progression. Multiple comparison corrections were not used to adjust the results of these alternative analyses.

Table 1 summarizes the overall clinical outcomes. At the time of the last follow-up, 81 of the patients (91%) were living, and 8 patients (9%) were dead at a mean±SD age of 8.6±2.0 years. Three of the deaths were associated with severe neurological progression; 4 deaths were due to complications of HSCT. It is important to note that HSCT methods and criteria have significantly improved since this study was initiated, and recent results with HSCT show a higher success rate and a more favorable outcome.10 Sixty-six patients (74%) were well at the time of the last follow-up, with normal neurological status and normal brain MRI results. Twenty-one patients (24%) developed MRI abnormalities. Ten patients (11%) developed neurological abnormalities (8 patients developed neurological abnormalities in addition to MRI abnormalities, and MRI results were not available for 2 patients). In 4 patients, neurological abnormalities first developed after HSCT. Sixty-four patients were less than 7 years old at the time of initiation of therapy, and it is only in this group that MRI or neurological abnormalities developed. All 25 patients who were aged 7 years or older at the time therapy began and who had thus, in accordance with entry criteria, escaped neurological involvement without dietary therapy continued to remain neurologically asymptomatic after initiation of therapy.

Table 2 provides more detailed information about each of the 23 patients who developed either MRI or neurological abnormalities. There were 8 patients for whom dates of onset of both MRI and neurological abnormalities were available. In these 8 patients, the MRI abnormalities preceded the neurological deficit at a mean±SD interval of 2.1±1.3 years.

ASSOCIATION BETWEEN C26:0 LEVELS AND MRI ABNORMALITIES

The Cox proportional hazards model with the time to MRI abnormality as the dependent variable and C26:0 LAUC (time-weighted average of C26:0, adjusting for follow-up duration) as the predictor demonstrated a significant as-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living</td>
<td>81 (91)</td>
</tr>
<tr>
<td>Deceased</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Neurologically normal and normal MRI results</td>
<td>66 (74)</td>
</tr>
<tr>
<td>MRI abnormalities and neurologically normal</td>
<td>13 (15)</td>
</tr>
<tr>
<td>MRI and neurological abnormalities*</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance image.

*Two patients had missing MRI results and had developed neurological abnormalities.
high LAUC values are predictive. As noted earlier, in this black dots, suggesting, unexpectedly, that either low or red Xs are substantially lower or higher than most of the values by 2-sided statistical test, from the values of the at-risk children who progressed systematically, the hazard ratio is 1.36; 95% CI, 1.07-1.72). For an increase of 0.1 µg/mL in the LAUC, with a confidence interval [CI], 2.04-228.1). The hazard ratio is because it is the ratio of odds of progression for a LO, as they compose the high-risk subset for developing CERALD. An association between LAUC and MRI abnormalities was also seen in these children (for 1 µg/mL, the hazard ratio = 10.82; \( P = .04 \); 95% CI, 1.10-106.84). The other TDCs representing more recent C26:0 estimates, such as the most recent value, the value 1 year before the present, and the average and largest values in the most recent year, did not significantly predict neurological or MRI progression.

ASSOCIATION BETWEEN C26:0 LEVELS AND NEUROLOGICAL ABNORMALITIES

In 8 of 10 patients who developed neurological abnormalities, an association between neurological abnormality and changes in plasma C26:0, as measured by LAUC, could not be evaluated owing to a lack of C26:0 measurements within 12 months of the event. Weighted average plasma C26:0 levels were significantly lower in patients who did not develop neurological abnormalities than in those who did (0.65±0.23 µg/mL vs 0.90±0.06 µg/mL, respectively; \( P = .007 \); weights were inversely proportional to the variance of each patient's average C26:0 level). Among the patients with neurological involvement, none normalized their plasma C26:0 levels (Table 3).

### Table 3. Clinical Data in 23 Patients Who Developed MRI or Neurological Abnormalities

<table>
<thead>
<tr>
<th>Patient No.*</th>
<th>Age at Initial Therapy, y</th>
<th>Age at First MRI Abnormality, y</th>
<th>Age at First Neurological Abnormality, y</th>
<th>Age at HSCT, y</th>
<th>Age at Death, y</th>
<th>Age at Last Follow-up, y</th>
<th>Neurological Status at Last Follow-up/Death†</th>
<th>HSCT Comment</th>
<th>Weighted Average Plasma C26:0 Level, µg/mL</th>
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<tr>
<td>1</td>
<td>1.10</td>
<td>6.58</td>
<td>7.81</td>
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<td>NA</td>
<td>9.10</td>
<td>22</td>
<td>NA</td>
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<tr>
<td>2</td>
<td>1.65</td>
<td>7.16</td>
<td>9.42</td>
<td>10.8</td>
<td>11.07</td>
<td>11</td>
<td>No engraftment</td>
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</tr>
<tr>
<td>3</td>
<td>1.52</td>
<td>Missing</td>
<td>6.92</td>
<td>7.52</td>
<td>7</td>
<td>8</td>
<td>NA</td>
<td>0.89</td>
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</tr>
<tr>
<td>4</td>
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<td>5.70</td>
<td>Normal</td>
<td>6.7</td>
<td>6.98</td>
<td>5.70</td>
<td>1 Severe GVH</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
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<tr>
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<td>6.10</td>
<td>7.95</td>
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<td>7.95</td>
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<td>10.18</td>
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<td>10.33</td>
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</tr>
<tr>
<td>9</td>
<td>2.72</td>
<td>10.50</td>
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<td>11.29</td>
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<tr>
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<td>4.18</td>
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<td>3.19</td>
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<td>6.00</td>
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<td>Severe GVH</td>
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<tr>
<td>15</td>
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<td>3.91</td>
<td>Normal</td>
<td>4.9</td>
<td>5.90</td>
<td>4.88</td>
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<tr>
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<td>7.74</td>
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<tr>
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<td>6.95</td>
<td>9.68</td>
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<td>17.43</td>
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<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: C26:0, hexacosanoic acid; CMV, cytomegalovirus; GVH, graft vs host reaction; HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance image; NA, not applicable.

*Patient number arranged in ascending order by age of therapy initiation.
†Excludes those neurological abnormalities that occurred after HSCT.
‡Values are post-HSCT data using a 25-point scale (Table 1) or qualitative description.

Association between the time to MRI abnormality and the LAUC, with a \( P \) value of .01 and a hazard ratio of 21.6 (95% confidence interval [CI], 2.04-228.1). The hazard ratio is large because it is the ratio of odds of progression for a 1-µg/mL increase in time-weighted average C26:0, which is a very large change. An increase of 0.1 µg/mL in the LAUC was associated with a 36% increase in instantaneous risk of developing MRI abnormalities (for a 0.1-µg/mL increase, the hazard ratio is 1.36; 95% CI, 1.07-1.72). For further interpretation of the above TDC analyses, the Figure was developed to display the values of the LAUC at the time of each MRI progression. For each of the 13 progressions displayed in the Figure (as the remaining 8 patients who had MRI abnormalities who had missing C26:0 measurements in the 12 months before the event), plotting symbols distinguish between the LAUC values of the child who progressed at that time and of the children at risk of progression but who had not yet done so (red Xs vs black dots, respectively). The 8 patients with an event but a missing LAUC at the time of event (no C26:0 measurement in the 12 months before the event) could not be included in the time-to-event analyses. A TDC is predictive if, at the same elapsed time since study entry, the value for the child who progressed differs systematically, by 2-sided statistical test, from the values of the at-risk children who did not progress. In the Figure, several of the red Xs are substantially lower or higher than most of the black dots, suggesting, unexpectedly, that either low or high LAUC values are predictive. As noted earlier, in this study none of the patients aged 7 years or older at baseline developed an MRI or neurological abnormality. Hence, we repeated these analyses in the 64 children who were younger than 7 years when they were first administered LO, as they compose the high-risk subset for developing CERALD. An association between LAUC and MRI abnormalities was also seen in these children (for 1 µg/mL, the hazard ratio = 10.82; \( P = .04 \); 95% CI, 1.10-106.84). The other TDCs representing more recent C26:0 estimates, such as the most recent value, the value 1 year before the present, and the average and largest values in the most recent year, did not significantly predict neurological or MRI progression.
ASSOCIATION BETWEEN CHANGES IN C26:0 AND ERUCIC ACID LEVELS

Thirty-six patients who had not taken LO before enrollment in the study were chosen for examination of this association. To detrend the 2 time series, simple exponential smoothing was employed for serial plasma C26:0 and erucic acid levels. Spearman rank correlation was calculated to evaluate the association between the paired, detrended values (within-person correlation). Median correlation and its 95% CI were generated using bootstrap resampling. The median (95% CI) for within-person correlation between plasma C26:0 and erucic acid was −0.63 (−0.35 to −0.84).

COMMENT

CLINICAL OUTCOME

Based on 89 boys followed up for a mean of 6.9 years, this is the first follow-up study of patients with ALD who had no neurological signs or symptoms and whose brain MRI results were normal at baseline. For reasons discussed in the introduction, all patients included in this study received VLCFA-lowering therapy. Mean ± SD age at the beginning of therapy was 4.8±4.1 years, with initiation in 64 patients before 7 years of age. Sixty-six patients (74%) remained free of neurological involvement. Twenty-one patients (24%) developed MRI abnormalities, and 8 patients (9%) developed both neurological and MRI abnormalities (Table 2). All MRI abnormalities preceded neurological abnormalities. In 9 patients whose MRI became abnormal, neurological status continued to be normal, in 1 instance for nearly 10 years (patient 23, Table 3). All patients with neurological abnormalities had the childhood cerebral phenotype. Longer follow-up is needed to assess whether these patients will progress to the AMN phenotype, but none did so during the study follow-up. The only remotely comparable data in untreated patients is a retrospective analysis of the histories in 443 symptomatic ALD patients who were members of families in which the ALD genotype and phenotype of every male was known.28 That study led to the estimate that approximately 35% of ALD patients develop symptoms before age 10 years. Comparability with the present group is limited because the time periods when these studies were conducted and the ages of the cohorts are different. Furthermore, in the historical sample, MRI studies were not available and neurological involvement was marked as present only when it was severe. It is likely, therefore, that 35% is an underestimate of the chance of neurological involvement by age 10 years in the untreated historical control group. The LO-treated cohort in this study appears to have had a more favorable course.

ASSOCIATION BETWEEN REDUCTION OF PLASMA C26:0 LEVELS AND CLINICAL OUTCOME

The time-weighted average (LAUC) of C26:0 levels since study entry was a significant predictor (P = .01; hazard ratio = 21.56; 95% CI, 2.04-228.1) of the time to neurologi...
logical progression. A statistically significant elevated risk of (more rapid) progression was seen in boys with an elevated LAUC. We anticipated that elevated C26 levels might be associated with quicker progression, but the presence of low as well high Xs (Figure) makes this hard to interpret in the absence of a randomized control group not receiving LO but with similar genetic and environmental factors. However, among patients who progressed to having a MRI abnormality, the overall outcome was better in those with low plasma C26:0 levels (Table 3). Notably, none of those who progressed had their average level of C26:0 lowered to within normal limits. Patients who had a neurological abnormality had significantly higher weighted average C26:0 levels than those who did not have an abnormality, suggesting that an LO-induced decrease in the C26:0 level could protect against inflammatory cerebral disease.

FACTORS ASSOCIATED WITH THE REDUCTION OF PLASMA C26:0 LEVELS

After removing overall trends in both series, plasma C26:0 levels were negatively correlated with plasma erucic acid levels (Spearman correlation, −0.63). Erucic acid is the active component of LO, and the plasma erucic acid level can thus be considered to be an index of the extent to which LO was consumed and absorbed. The observed correlation suggests that compliance with LO intake is a significant factor in the reduction of the plasma C26:0 level. The degree of reduction of fat intake is a second factor. In the current study, we aimed to limit fat intake from other sources to less than 15% of total calories, and the dietary intake records indicate that most patients were able to comply with this. However, our experience with other ALD patients and that of Rizzo et al16 indicate that total fat intake in excess of 30% to 35% of total calories may counteract or nullify the C26:0-reducing effect of LO. There was no correlation between the reduction of the C26:0 level and the nature of the ABCD1 mutation or the phenotypic pattern of affected relatives (data not shown).

BIOLOGICAL INTERPRETATION AND CLINICAL RELEVANCE

The association between the LAUC and the development of MRI abnormalities in asymptomatic patients with ALD suggests that long-term reduction of C26:0 levels reduces the risk of developing brain MRI abnormalities in asymptomatic boys with ALD. Statistical summaries (TDCs) that emphasized the most recent year of C26:0 observations did not show this significant association, suggesting that long-term elevation of the plasma C26:0 level is more deleterious, and hence long-term lowering of plasma VLCFA levels should be more beneficial. This is clinically significant because brain MRI abnormalities have been shown to correlate with neurological and neuro-psychological deficits and prognosis in ALD.20 Despite the apparent bidirectional association between C26:0 levels and time to progression (Figure), our results imply an elevated risk of developing MRI abnormalities with an increase in time-weighted C26:0 average levels; for a 0.1-µg/mL increase in C26:0 LAUC, the associated hazard ratio was 1.36 and the 95% CI was 1.07 to 1.72. Most patients who take LO in a carefully supervised program reduce this level by 0.4 to 0.6 µg/mL, suggesting that a 2-fold reduction of risk can be achieved. Several limitations apply to these conclusions:

1. Our follow-up period was relatively short. It is not known how long the preventive effect with respect to CERALD will persist or whether the therapy alters the risk for AMN in adulthood.

2. We have a limited understanding of the factors that cause the profound differences between the inflammatory CERALD phenotype and the noninflammatory AMN phenotype. Our studies are relevant only to the former because AMN manifests only rarely before the age at which our follow-up closed. Past experience with hundreds of untreated ALD patients indicates that, irrespective of plasma C26:0 levels, half of them never develop CERALD and thus for unknown reasons appear resistant to this phenotype, although nearly all develop AMN if they live to adulthood.1,9,10 The patients without events with high plasma C26:0 levels shown in the Figure perhaps represent this group. On the basis of our data, we hypothesize that lowering plasma C26:0 levels reduces the risk of CERALD in those patients who are not innately resistant to it, but, as noted, the prevention is not absolute. The mechanism of the preventive effect is poorly understood owing to our inability to measure brain C26:0 levels in vivo. In studies of postmortem tissue of LO-treated patients, the effect on C26:0 levels in the brain has been variable, and it was questioned whether the oil crossed the blood-brain barrier.31,32 However, it has since been shown that 14C-labeled erucic acid does enter the brain in rodents.33

THERAPEUTIC RECOMMENDATION

We recommend that LO therapy be offered to male patients with ALD who are neurologically asymptomatic, have normal brain MRI results, and are at risk of developing CERALD. This recommendation is based on strongly suggestive, albeit not fully definitive, evidence of a preventive effect combined with our awareness of the severe prognosis of the untreated patients with CERALD. Another important factor is the absence of serious adverse effects in our study population. At present, such patients are identified by plasma VLCFA assay-screening of at-risk relatives of patients known to have ALD or idiopathic Addison disease.34 Neonatal screening, now under consideration, would identify many more. It has been shown that the risk for developing CERALD is greatest in boys who are younger than 7 years31; this risk diminishes after 10 years of age, and still more after age 14 years, but it never vanishes completely.30 The patients who are younger than 7 years represent prime candidates for this therapy. We hypothesize that intensive LO therapy during the ages at which the risk for CERALD is greatest may protect against this phenotype until they reach the ages at which the risk for CERALD diminishes. We do not recommend initiation of therapy before 12 months of age because LO therapy may lower the
levels of docosahexaenoic acid (DHA) in ALD patients. Docosahexaenoic acid plays a major role in early retinal and brain development, particularly during the first year of life, and DHA supplementation might not fully restore normal patterns at this critical early developmental stage.

Lorenzo's oil therapy must be part of a carefully supervised program that includes a pediatrician, nurse coordinator, nutritionist, a biochemical and clinical laboratory, and careful attention to social and educational issues. Fat intake from sources other than the oil should not exceed 15% of total calories. Supplements of essential fatty acids, particularly DHA, should be provided. Monitoring of platelet counts, levels of VLCFA, erucic acid, essential fatty acids, DHA, liver enzymes, adrenal function, brain MRI, and neurological function is required. Because of an apparent dose-response effect, the aim is to achieve substantial and sustained reduction in plasma C26:0 levels. Our results indicate that a 0.6-µg/mL reduction in plasma C26:0, a goal we think is practical, is associated with an approximately 2-fold reduction in the risk of developing MRI abnormalities. Lack of any significant association with recent C26:0 level estimates suggest that transient C26:0 reduction may be insufficient to protect against CERALD. The moderate reduction of the platelet count that may occur in up to 30% of patients can be managed successfully as described in the “Methods” section. Monitoring of brain MRI results is critically important. We recommend that brain MRIs be obtained at 6-month intervals between 3 and 10 years of age and yearly thereafter, and that those patients who develop progressive MRI abnormalities be considered for H SCT in accordance with the recommendations formulated by Peters et al. Adrenal function must be monitored. Eighty percent of asymptomatic patients with ALD develop evidence of adrenal insufficiency, and if present, adrenal hormone replacement therapy should be provided. This 3-pronged therapeutic approach can improve the prognosis of this devastating disease.

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Conflict of Interest: Mr. Odone, inventor of Lorenzo’s oil, has licensed the patent to Croda Chemicals Europe Ltd, East Yorkshire, England. As president of the Myelin Project, he is in frequent contact with ALD families. To avoid any potential conflict of interest, the agreement with Croda provides that any royalties arising from the sale of Lorenzo’s oil will accrue to the Myelin Project, a 501(c)3 charitable organization.

REFERENCES

7. Ito M, Blumberg BM, Mock DJ, et al. Potential environmental and host-bioSTatic issues. Fat intake from sources other than the oil should not exceed 15% of total calories. Supplements of essential fatty acids, particularly DHA, should be provided. Monitoring of platelet counts, levels of VLCFA, erucic acid, essential fatty acids, DHA, liver enzymes, adrenal function, brain MRI, and neurological function is required. Because of an apparent dose-response effect, the aim is to achieve substantial and sustained reduction in plasma C26:0 levels. Our results indicate that a 0.6-µg/mL reduction in plasma C26:0, a goal we think is practical, is associated with an approximately 2-fold reduction in the risk of developing MRI abnormalities. Lack of any significant association with recent C26:0 level estimates suggest that transient C26:0 reduction may be insufficient to protect against CERALD. The moderate reduction of the platelet count that may occur in up to 30% of patients can be managed successfully as described in the “Methods” section. Monitoring of brain MRI results is critically important. We recommend that brain MRIs be obtained at 6-month intervals between 3 and 10 years of age and yearly thereafter, and that those patients who develop progressive MRI abnormalities be considered for H SCT in accordance with the recommendations formulated by Peters et al. Adrenal function must be monitored. Eighty percent of asymptomatic patients with ALD develop evidence of adrenal insufficiency, and if present, adrenal hormone replacement therapy should be provided. This 3-pronged therapeutic approach can improve the prognosis of this devastating disease.

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