A0001 in Friedreich Ataxia: Biochemical Characterization and Effects in a Clinical Trial

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ABSTRACT: This study tested the ability of A0001 (α-tocopheryl quinone; EPI-A0001), a potent antioxidant, to improve in vitro measures, glucose metabolism, and neurological function in Friedreich ataxia. We used an in vitro study of protection from cell toxicity followed by a double-blind, randomized, placebo-controlled trial of 2 doses of A0001 in 31 adults with Friedreich ataxia. The primary clinical trial outcome was the Disposition Index, a measure of diabetic tendency, from a frequently sampled intravenous glucose tolerance test, evaluated 4 weeks into therapy. Secondary neurologic measures included the Friedreich Ataxia Rating Scale. A0001 potently inhibited cell death in Friedreich ataxia models in vitro. For the clinical trial, mean guanine-adenine-adenine repeat length was 699, and mean age was 31 years. Four weeks after treatment initiation, differences in changes in the Disposition Index between subjects treated with A0001 and placebo were not statistically significant. In contrast, a dose-dependent improvement in the Friedreich Ataxia Rating Scale score was observed. Patients on placebo improved 2.0 rating scale points, whereas patients on low-dose A0001 improved by 4.9 points ($P = .04$) and patients on a high dose improved by 6.1 points ($P < .01$). Although A0001 did not alter the Disposition Index, it caused a dose-dependent improvement in neurologic function, as measured by the Friedreich Ataxia Rating Scale. Longer studies will assess the reproducibility and persistence of neurologic benefit.

Key Words: cerebellum; dorsal root ganglion; antioxidant; mitochondrion; disposition index

Additional Supporting Information may be found in the online version of this article.

David R. Lynch, Steven M. Willi, and Robert B Wilson contributed equally to the present work.

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Friedreich ataxia (FRDA) is an autosomal recessive disorder associated with progressive ataxia, scoliosis, and cardiomyopathy. Many patients also develop diabetes mellitus and insulin resistance. FRDA is caused by homozygous mutations in the FXN gene, with 97% of patients carrying GAA repeat expansions in the first intron on both alleles of the FXN gene. This results in decreased expression of the mitochondrial protein frataxin. Reduced frataxin expression impairs the function of mitochondrial iron-sulfur-cluster-containing enzymes and leads to accumulation of iron in the mitochondrial matrix. FRDA patient–derived cells have increased susceptibility to oxidative stress; therefore, it is believed that FRDA patients may benefit from treatment with agents that improve mitochondrial respiratory chain function such as coenzyme Q10 (CoQ) and idebenone. However, in clinical trials these agents have not improved neurologic function or slowed progression. A0001, a novel agent that may improve mitochondrial function, has structural similarities to CoQ10 and idebenone but superior bioavailability that might make it more efficacious. At present, there is no FDA-approved treatment for FRDA.

Phase II studies frequently use biomarkers as primary outcome markers, but few validated biomarkers are available in FRDA. Abnormalities in glucose handling are a core component of FRDA and are rationally linked to abnormal mitochondrial function. Thus, detailed assessment of glucose metabolism could reveal relevant biomarkers of mitochondrial function in FRDA and lend insight into the efficacy of agents like A0001. In the present study, we assessed whether A0001 could protect cells in an FRDA model in vitro and reverse the abnormalities of glucose metabolism in FRDA patients, with parallel assessment of neurological and biochemical measures during a 1-month trial.

Patients and Methods

In Vitro Studies

In vitro studies were performed using the I154F frataxin point-mutation model, generously provided by Dr. Helène Puccio. This model was derived through the stable integration and expression of human frataxin harboring the disease-associated missense mutation I154F in murine fibroblasts from which both copies of the murine frataxin gene were deleted. The model exhibits virtually all the biochemical hallmarks of FRDA, including mitochondrial iron accumulation, loss of iron-sulfur cluster enzyme activities, and sensitivity to iron and oxidative stress. 48 well plates were seeded 15,000 cells/well in standard medium. Ferric ammonium citrate (FAC; Sigma; iron content 16.5%–18.5%) was added (final concentration, 20 μg/mL). The following day, l-buthionine (S,R)-sulfoximine (BSO) was added (50 μM final concentration) and followed 2 hours later by A0001 or idebenone. Forty-eight hours later, cells were washed with phosphate-buffered saline (PBS), and viability was assessed using the CellTiter-Glo assay kit (Promega). The data were analyzed with GraphPad Prism version 5 using a sigmoidal dose response with variable slope (4 parameters).

Clinical Trial Overview

We performed a double-blind, randomized, placebo-controlled trial of A0001 on subjects with FRDA. The study was conducted at a single site, the Children’s Hospital of Philadelphia (CHOP). The primary objective investigated was whether 28 days of therapy with A0001 had a discernable impact on functional, biochemical, and neurological measures of FRDA. In addition, we examined the tolerability, safety, and pharmacokinetics of A0001 in this population. This study was performed following approval of the CHOP institutional review board.

Study Drug

A0001 was prepared as elongated hard-gelatin white opaque capsules containing either 250 or 170 mg A0001 in olive oil. Matching placebo capsules contained 0.01% beta-carotene in olive oil. Beta-carotene was added as a colorant to match the color of the A0001 capsules and maintain blinding.

Subject Recruitment and Inclusion Criteria

Subjects were recruited using the Friedreich’s Ataxia Research Alliance database, listing on ClinicalTrials.gov (NCT01035671), and through the clinical practices of the principal investigator and his collaborators. Subjects were between ages 18 and 60, with genetically confirmed FRDA. For screening, subjects (n = 45) underwent a standard 75-g (or 1.75 g/kg body weight) oral glucose tolerance test (OGTT). As the hope was to target individuals with modest degrees of aberrant glucose metabolism, inclusion criteria included: fasting blood glucose between 5.5 and 7 mmol/L. (between 100 and 126 mg/dL), a 2-hour plasma glucose level between 7.8 and 11.1 mmol/L (between 140 and 200 mg/dL) after OGTT, and/or an
Oral Glucose Insulin Sensitivity (OGIS) index\(^{19}\) \(\leq 450\) mL/min/m\(^2\). Patients were excluded if they had a diagnosis of diabetes requiring therapy with insulin or other hypoglycemic agent or had clinically significant cardiovascular disease. Subjects were required to abstain from use of coenzyme Q, idebenone, or vitamin E for at least 2 weeks preceding baseline through the 28-day administration of the study drug.

Once subjects met screening criteria, they were randomized within 21 days of baseline to 1 of 3 potential treatment arms: placebo, low-dose A0001 (510 mg), or high-dose A0001 (750 mg). Study medication was taken with meals for 28 consecutive days. Subjects were evaluated clinically and biochemically on days 14 and 28. Blood samples for safety assessment were collected on days 4, 7, 11, 14, 17, 21, 24, and 28. Subjects were contacted by telephone 1 week following their last dose of the study drug for safety monitoring.

**Primary and Secondary Outcome Measures**

The primary end point was the change in Disposition Index (DI) from an insulin-modified, frequently sampled intravenous glucose tolerance test (fsIVGTT). In this situation, the DI is a measure of beta cell compensation for insulin resistance and consistently declines prior to the development of diabetes.\(^{21}\) Secondary outcome measures included additional parameters from the fsIVGTT (sensitivity index [\(S_v\)], glucose effectiveness (\(S_e\)), and acute insulin response (AIR\(_g\)), other metabolic measures of glucose homeostasis (fasting glucose, insulin, lactate, HbA1C, plasma 1,5-anhydroglucitol [1,5-AG]), as well as other relevant biochemical (Specific Activity of Complex I in whole blood [Mitoscience, Eugene, OR], frataxin levels in blood, plasma coenzyme Q levels, plasma vitamin E levels), neurological (Friedreich ataxia rating scale [FARS]),\(^{22-24}\) Timed 25 Foot Walk [T25FW], 9-Hole Peg Test [9HPT], Low Contrast Sloan Letter Acuity [LCSLA]), and clinical (Global Impression of Clinical Severity (GICS), Modified Fatigue Impact Scale (MFIS), activities of daily living [ADLs], SF36) measures.

**Sample Size Calculation and Statistical Analyses**

Sample size was predicated on A0001 inducing a 25% or greater improvement in the primary end point. The minimum number of subjects who would be sufficient to demonstrate a 25%–30% improvement in the primary outcome with at least 80% statistical power would be 10 subjects per arm. An ANCOVA model was used to evaluate the change of efficacy measures from baseline, including term of treatment and baseline score as covariates.\(^{26}\) If a subject discontinued the study prior to day 28, the last observation carried forward method was used to impute data. For glucose measures, data were analyzed and presented after log-transformation to allow parametric analysis. FARS scores, SF36, ADL, MFIS, and GICS scales, and performance measures are presented without transformation. In addition, a non-parametric analysis-of-covariate model was used for the change from baseline for the primary end point, the DI. Post hoc linear regression models were used to assess whether use of CoQ or vitamin E immediately preceding the study predicted baseline levels of these 2 agents, accounting for age. Analogous models were used to test whether A0001 therapy predicted plasma CoQ and vitamin E levels after 28 days of the study drug, accounting for baseline levels.

**Results**

**In Vitro Study**

We tested the in vitro effects of A0001 using the I154F frataxin point-mutation model.\(^{18}\) At low concentrations, simultaneous treatment of these cells with the combination of iron (as ferric ammonium citrate) and BSO (which inhibits glutathione synthesis) resulted in loss of viability and almost complete cell death over 72 hours. A0001 prevented this cell death in a dose-dependent manner, with an EC\(_{50}\) of 16.6 nM, 15-fold lower than that of idebenone (Fig. 1). The functional effect of A0001 was ascertained using the tetrazolium dye WST-1 as described in the Patients and Methods section; on a per-cell basis, A0001 improved WST-1 reduction by 40% at 1 \(\mu\)M and by 30% at 100 nM (\(P < .001\) in both cases).

**Clinical Trial: Screening and Baseline Results**

A total of 45 subjects were screened between December 1, 2009, and November 1, 2010; 34 subjects
met inclusion criteria based on glucose-metabolism criteria. One subject failed the criteria based on an elevated baseline troponin level consistent with significant cardiomyopathy. Two subjects withdrew or were withdrawn after screening based on the inability to perform study procedures (Fig. 2). For the 14 excluded subjects, median shorter GAA repeat length was 620, and median age was 28 years.

Subjects were randomized to 3 groups (Supplementary Table 1). In general, the groups were similar in composition, particularly the placebo and high-dose groups. The low-dose cohort were slightly older and had a larger BMI, shorter GAA repeat length, and lower FARS exam score, but these were not statistically significant.

Safety and Tolerability of A0001

Although most subjects experienced at least 1 adverse effect (AE; Supplementary Table 2), few were felt related to study drug, suggesting that A0001 was well tolerated. No drug-related severe AEs were noted, and other AEs were generally low grade and found equally in groups. One subject was discontinued when an elective dental procedure (unrelated to the protocol) was performed. Interestingly, fatigue, a common symptom of FRDA, was somewhat lower in the high-dose group (1 subject vs 3 for placebo and 4 for low dose; not significant).

As expected based on phase I data, A0001 slightly prolonged PT and INR values (Fig. 3A,B). A minimal effect was noted on aPTT as well. This effect was dose dependent and maximal 4–10 days after initiation of A0001. Levels gradually returned toward normal, such that on day 28 INR levels were normal in the low-dose group and slightly elevated in the higher-dose group. No significant bleeding events were recorded, even in the subject who had a dental procedure performed on high-dose A0001.

Effect on Plasma and Lymphocyte Markers

We also examined the effect of A0001 on markers of mitochondrial function in whole blood (complex I) and plasma levels of the endogenous potential antioxidants CoQ and vitamin E (Fig. 4), whose levels may alter response in FRDA. Complex I level did not change during the study (not shown).\textsuperscript{27} Using linear

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**FIG. 2.** COHORT Enrollment diagram. 45 subjects were screened and 31 randomized in the study. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
regression models accounting for subject age, levels of CoQ and vitamin E at the initiation of the study were not predicted by whether subjects were taking such cofactors/vitamins exogenously at screening ($P = .14$ for CoQ, $P = .35$ for vitamin E). This suggests that the washout period was sufficient to restore at least plasma levels to normal following exogenous administration. Interestingly, age independently predicted vitamin E ($P = .001$) but not CoQ ($P = .13$) levels at baseline. Levels of CoQ and vitamin E did not predict baseline neurological status in linear regression models accounting for age and GAA repeat length, showing no link between these levels and long-term variability in FRDA. Following administration of the study drug, there was no arithmetic difference in levels of vitamin E and CoQ based on study drug using ANCOVA models. In contrast, when analyzed by linear regression models examining final levels accounting for baseline and treatment group, levels of vitamin E ($R^2 = 0.81$, $P < .001$) and CoQ ($R^2 = 0.64$, $P < .001$) after 28 days of therapy were predicted by baseline levels. In addition, treatment with A0001 predicted a higher level of CoQ after 28 days ($P = .024$). When we compared the baseline and 28-day levels of CoQ graphically, the slope of the line and the correlation coefficient changed in the high-dose group, consistent with A0001 administration modulating endogenous plasma CoQ levels (Fig. 4B). No effect of A0001 dose on vitamin E levels after 28 days was noted in linear regression models ($P = .68$; Fig. 4A).

**Effect of A0001 on Glucose Handling and Neurological Outcome Measures**

When the primary outcome measure, the DI from the fsIVGTT, was compared between groups, no significant differences were noted after 28 days of treatment (Table 1A). Similarly we found no significant differences between groups in any secondary outcome measure calculated from the fsIVGTT. We also examined differences in fasting glucose, HbA1c, and 1,5-anhydroglucatol (a measure of postprandial hyperglycemia). Although fasting glucose and HbA1c exhibited a trend toward a favorable dose–response relationship, none was significant in our small sample.

In contrast, A0001 produced a significant change in the exam-based neurologic measure, the FARS. There was a dose-dependent, statistically significant improvement in FARS score of 4 points greater than placebo in the high-dose group (Table 1B). Placebo-group response was about 2 units, consistent with that noted in previous studies. Improvement in the high-dose A0001 group was roughly equal (inversely) to the amount of progression seen over 1–2 years in FRDA. The improvements were noted on several subscales of the FARS (although it reached significance on none),

![FIG. 3. Effect of A0001 on clotting parameters. A0001 prolonged clotting parameters in a dose-dependent manner. The effect was much greater on PT and INR (A) values than on PTT (B) values and was maximal 4–8 days after drug initiation.](image1)

![FIG. 4. Effect of A0001 on plasma vitamin E and coenzyme Q levels. Vitamin E (A) and coenzyme Q (B) levels were compared before and after 28 days of therapy with A0001. Posttreatment vitamin E levels correlated with baseline levels; baseline level, but not treatment group, predicted posttreatment level. In contrast, coenzyme Q levels diverged after therapy, and both baseline level and treatment group predicted posttreatment level in linear regression analysis. Both doses of A0001 were associated with a higher coenzyme Q level on day 28. The dotted line shows equal values before and after treatment.](image2)
and among those subjects who showed at least 5 points of improvement, a similar number improved on each subscale (data not shown). Improvement in FARS score was relatively uniform: 8 of 10 subjects on high dose and 7 of 11 subjects on low dose improved greater than 3.5 FARS points (roughly 1 year’s progression), but only 3 of 10 subjects on placebo. Similarly, 6 of 10 subjects on high dose and 6 of 11 on low dose improved by more than 6.1 points (2 years’ progression), whereas no patient on placebo improved to this degree. In addition, sensitivity analyses performed by omission of single subjects in the high-dose group had no effect on the results (Supplementary Fig. 1). The change in FARS score remained significant with omission of each subject, showing that the results were not driven by single subjects. Interestingly, other neurologic measures (performance measures, analyzed as their reciprocals) and subjective ADL and quality-of-life scales showed no consistent pattern (Table 1C). No relation of baseline CoQ or vitamin E level was noted (not shown).

**Discussion**

The present study reveals the potential role of A0001 as a therapeutic agent in FRDA. This reflects not only the in vitro data in a well-characterized cellular model of FRDA, but improvement in neurologic function as measured by the FARS exam in a phase II trial. No improvement was noted in the primary outcome measure, the DI, or in an extensive examination of other glucose-handling measures. In addition, no other neurologic measures showed a clear trend in this short study. Still, the improvement in FARS was statistically significant and of a clinically significant magnitude.

The clinical trial results are reminiscent of those noted in phase II studies with idebenone, an agent that is similar in structure to A0001. Idebenone produced dose-dependent improvement in neurologic function over a relatively short period in a restricted cohort, but such improvements were not observed in larger, multicenter studies. In contrast, the improvement in

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**TABLE 1. Analysis of change in measures on day 28**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo (n=10)</th>
<th>0.5 g BID (n=11)</th>
<th>0.75 g BID (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Glucose measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposition index LS mean</td>
<td>0.26</td>
<td>0.35</td>
<td>0.44</td>
</tr>
<tr>
<td>Sensitivity index LS mean</td>
<td>0.56</td>
<td>-0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Glucose effectiveness LS mean</td>
<td>0.24</td>
<td>0.35</td>
<td>-0.19</td>
</tr>
<tr>
<td>Acute insulin response LS mean</td>
<td>0.12</td>
<td>0.29</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo (n=10), mean ± SD</th>
<th>0.5 g BID (n=11), mean ± SD</th>
<th>0.75 g BID (n=10), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. FARS exam and subscales</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall FARS</td>
<td>-2.03 ± 2.35</td>
<td>-4.92 ± 3.4, P=0.040</td>
</tr>
<tr>
<td>Subscores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>-0.10 ± 0.89</td>
<td>-0.29 ± 0.85</td>
</tr>
<tr>
<td>Upper limb</td>
<td>-2.04 ± 2.4</td>
<td>-2.34 ± 2.5</td>
</tr>
<tr>
<td>Lower limb</td>
<td>0.30 ± 1.6</td>
<td>-1.01 ± 1.43, P=0.13</td>
</tr>
<tr>
<td>Peripheral</td>
<td>-0.08 ± 0.51</td>
<td>-0.81 ± 2.33</td>
</tr>
<tr>
<td>Upright</td>
<td>0.37 ± 2.51</td>
<td>-0.86 ± 2.24</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Placebo (mean ± SD)</th>
<th>0.5 g BID (mean ± SD)</th>
<th>0.75 g BID (mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td><strong>C. Performance measures, questionnaire, and clinical measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/T25W</td>
<td>-0.00013 ± 0.00587</td>
<td>0.0092 ± 0.0120</td>
</tr>
<tr>
<td>1/9HPT</td>
<td>0.00056 ± 0.00136</td>
<td>0.00084 ± 0.00147</td>
</tr>
<tr>
<td>ADL LS mean</td>
<td>-1.27 ± 2.66</td>
<td>-1.63 ± 2.31</td>
</tr>
<tr>
<td>SF36 PFSLS mean</td>
<td>3.26 ± 5.0</td>
<td>-4.77 ± 5.7</td>
</tr>
<tr>
<td>MRS LS mean</td>
<td>-11.4 ± 18.0</td>
<td>-11.9 ± 17.0</td>
</tr>
<tr>
<td>GICS LS mean</td>
<td>0.00</td>
<td>-0.00</td>
</tr>
</tbody>
</table>

Data are presented as least squares mean change from baseline after log-transformation for glucose measures and without log-transformation for FARS scores, performance measures, and questionnaires. P values (based on ANCOVA models) < .2 (when compared with placebo) are shown.
neurologic function observed with A0001 treatment, shown here in a relatively unrestricted adult cohort, is substantially greater in magnitude than that noted in phase II or III trials of idebenone. This matches the higher potency of A0001 in vitro and suggests that this molecule deserves further development for use in FRDA and other mitochondrial disorders. Conceivably, A0001 might improve mitochondrial function in neurons that are metabolically impaired, leading to an improvement in FARS score.

Although no improvement was noted in the primary outcome measure and in some neurologic measures, a variety of factors may have contributed to these results. First, the length of the trial was quite short. Second, the overall insulin resistance of the study population was less than that seen in previous reports, perhaps lowering the potential drug-related improvement. 3–5 This, combined with the relatively high intrasubject variability observed, may have limited the capacity to demonstrate significant results in a small study. In addition, the randomization did not completely match groups, as noted by the slightly different ages and GAA repeat lengths of the groups. The diverse nature of the cohort may have contributed to the relative sensitivity of different measures. In the overall cohort, FARS scores clustered around 60–70, the range in which subjects are losing ambulation. The FARS is likely to be most sensitive to change in this region, as it is weighted toward ambulation. In contrast, ADL scales and performance measures capture dysfunction in different ranges. Performance measure composites were not assessed in this group, given the small size of the cohort; such measures are more likely than single performance measures to capture the complete magnitude of response. 22–24

In the clinical study, CoQ and vitamin E levels were used to understand better whether endogenous antioxidants might provide markers of the mechanism behind the effects of A0001. At baseline, CoQ and vitamin E levels were heterogeneous across the cohort but were not predicted by recent use of either of these agents. This suggests that the 2-week washout period is sufficient for allowing the return of CoQ levels to baseline. Interestingly, baseline CoQ and vitamin E levels did not predict response to A0001 on the FARS score, in contrast to a previous report suggesting that baseline CoQ levels alter response to long-term administration of CoQ. 12 In addition, baseline CoQ levels did not predict baseline neurologic status. If such levels reflect long-term CoQ metabolism in subjects, the variability of such metabolism is unlikely to modulate phenotypic severity in FRDA. However, A0001 appeared to alter endogenous levels of CoQ but not a-tocopherol (vitamin E). Whether this reflects upregulation of CoQ synthesis (to balance the increased tocopherol-like activity provided by A0001, for example) or a decrease in catabolism or clearance of CoQ is unclear.

Overall, A0001 was safe, with no major adverse events. Although clotting times were prolonged, this appears to be transient, and no bleeding events occurred. Individuals with FRDA may take anticoagulants when significant cardiomyopathy is present, suggesting that clinical use of A0001 may complicate coadministration of traditional anticoagulants such as warfarin. This favorable profile, along with the data suggesting the potential benefit of A0001, makes it a worthy candidate for further investigation in FRDA in a larger, longer clinical trial.

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