Antioxidant Treatment of Patients With Friedreich Ataxia

Four-Year Follow-up

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Background: Decreased mitochondrial respiratory chain function and increased oxidative stress have been implicated in the pathogenesis of Friedreich ataxia (FRDA), raising the possibility that energy enhancement and antioxidant therapies may be an effective treatment.

Objective: To evaluate the long-term efficacy of a combined antioxidant and mitochondrial enhancement therapy on the bioenergetics and clinical course of FRDA.

Design: Open-labeled pilot trial over 47 months.

Patients: Seventy-seven patients with clinical and genetically defined FRDA.

Intervention: A combined coenzyme Q10 (400 mg/d) and vitamin E (2100 IU/d) therapy of 10 patients with FRDA over 47 months.

Main Outcome Measures: Clinical assessment using echocardiography and the International Cooperative Ataxia Rating Scale and cardiac and skeletal muscle bioenergetics as assessed using phosphorus P 31 magnetic resonance spectroscopy.

Results: There was a significant improvement in cardiac and skeletal muscle bioenergetics that was maintained throughout the 47 months of therapy. Echocardiographic data revealed significantly increased fractional shortening at the 35- and 47-month time points. Comparison with cross-sectional data from 77 patients with FRDA indicated the changes in total International Cooperative Ataxia Rating Scale and kinetic scores over the trial period were better than predicted for 7 patients, but the posture and gait and hand dexterity scores progressed as predicted.

Conclusion: This therapy resulted in sustained improvement in mitochondrial energy synthesis that was associated with a slowing of the progression of certain clinical features and a significant improvement in cardiac function.

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FRIEDREICH ATAXIA (FRDA) is an autosomal recessive disease characterized clinically by a progressive gait and limb ataxia, absence of deep tendon reflexes, and loss of position and vibration sense in the lower limbs. Skeletal abnormalities, cardiac hypertrophy, and, to a lesser degree, diabetes mellitus and optic atrophy are also present in patients with FRDA. In 95% of patients the cause is a homozygous expansion of the GAA repeat in intron 1 of the FRDA gene that results in deficiency of its protein product, frataxin,1 which is localized to the mitochondrion. Data from a yeast frataxin homologue knockout model suggest that decreased iron-sulfur cluster synthesis may, indeed, be the primary defect, and that this leads to elevated iron levels and oxidative damage.2

The presence of defective mitochondrial oxidative phosphorylation in FRDA pathology has been confirmed in vivo in patients with FRDA using phosphorus P 31 magnetic resonance spectroscopy (31P MRS) investigations of cardiac and skeletal muscle bioenergetics.3,4 Likewise, there is evidence of increased oxidative damage3 in patients with FRDA, which may increase with disease progression. The involvement of mitochondrial respiratory chain dysfunction and oxidative stress in FRDA pathogenesis suggests FRDA may be amenable to treatment with a combined antioxidant and bioenergetic therapy.6

We have shown that combined coenzyme Q10 (CoQ10) and vitamin E therapy resulted in a significant improvement in cardiac and skeletal muscle energy metabolism in 10 patients with FRDA after 3 months of treatment.8 This is a long-
Table 1. Influence of CoQ10 and Vitamin E Therapy on the Parameters of Friedreich Ataxia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Serum Vitamin E Level, mg/dL</th>
<th>Serum CoQ10 Level, µg/mL</th>
<th>31P MRS Heart PCr/ATP Ratio</th>
<th>31P MRS Skeletal Muscle, Vmax</th>
<th>IVSd, cm</th>
<th>PWd, cm</th>
<th>FS, %</th>
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| Initial     | Mean Therapy                  | Initial                  | Mean Therapy                | Initial                        | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy | Initial | Mean Therapy 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The heart and skeletal muscle $^{31}$P MRS analyses were performed throughout the trial period (Figure 1). Cardiac $^{31}$P MRS was not performed on patient 5 (because the patient had asymptomatic atrial fibrillation). Skeletal muscle $^{31}$P MRS studies were not performed on patient 7 after baseline data (because of the patient’s receiving botulinum toxin injections in both calves) or on patients 5 and 6 at the 47-month point (because these patients were unable to perform the skeletal muscle exercise).

The significant improvement in the cardiac phosphocreatine–adenosine triphosphate (PCr/ATP) ratio evident after 3 months of combined CoQ$_{10}$ and vitamin E therapy was maintained at all assessments up to 47 months (Figure 1A). Before therapy, 5 patients (patients 6 through 10) showed left ventricular hypertrophy (LVH), (intraventricular septal [IVS$_d$], and/or posterior wall [PW$_d$] thickness in diastole $\geqslant$1.1 cm). The average improvement in cardiac PCr/ATP over the trial period was similar in the patients with (mean±SD, 173.6%±91.1% of pretherapy values) or without LVH (mean±SD, 206.7%±88.5% of pretherapy values) (Table 1).

The resting calf muscle PCr/inorganic phosphate (Pi) ratios improved throughout the therapy reaching control values after 23 months (Figure 1B). The improvement in the maximum rate of mitochondrial ATP synthesis (maximum velocity [Vmax]) measured at the end of exercise was maintained throughout the 47 months of the trial (Figure 1C).

In comparison with the pretherapy values the mean IVS$_d$ and PW$_d$ thickness during therapy showed a decrease in 6 and 5 patients, respectively, but many of these changes were within the variation seen with this technique. When expressed as the percentage change from the pretherapy values, there was no overall change in the IVS$_d$ or PW$_d$ values throughout the 47-month trial (Figure 2A and B). Fractional shortening showed a significant increase at the 35- and 47-month assessments (Figure 2C). At these time points, fractional shortening was not influenced by the presence of LVH (Table 1).

The patients’ ICARS scores were normalized by expressing them as a percentage of the pretherapy ICARS scores. As a group, the total ICARS scores did not increase over the trial period (Figure 3A); however, the posture and gait scores deteriorated significantly from the pretherapy scores (Figure 3B), and the kinetic scores improved (Figure 3C); this occurrence did not reach statistical significance. The speech and ocular motor scores did not show any statistically significant change over the course of the therapy (data not shown).

The total ICARS and component scores for each patient obtained over 47 months were plotted against patient age to obtain the rate of change during the trial period. In the absence of longitudinal natural history data, we used cross-sectional ICARS data from a group of 77 heterogeneous patients with FRDA to predict the clinical course of the disease. These patients were divided into 4 groups (A-D) according to their GAA$_1$ sizes, to allow for the influence of genetic severity on clinical progression, and the rate of clinical change estimated for each group using linear regression analysis (Table 2). These data will be presented in more detail elsewhere (P.E.H., unpublished data, 2004). Similarly the rates of change were determined for each patient over the 47 months of the trial period and compared with those predicted for the appropriate cross-sectional group. The rate of change in total ICARS scores were better than predicted in 6 patients (patients 1, 2, 4, 7, 9, and 10) and, indeed, demonstrated an improvement. The rate of change in the kinetic scores also demonstrated an improvement in these 6 patients, and in patient 3, the scores remained stable throughout the trial period (Table 2). The change in posture and gait scores were similar to the predicted scores for all except patient 5 who showed an improvement (Table 2). The speech (Table 2) and ocular motor scores (data not shown) were small and variable mak-
The longitudinal data from the 10 patients in the trial demonstrated a decline in dominant hand dexterity that was equal to or greater than the decline predicted from the cross-sectional data (Table 2).

**COMMENT**

Combination of high doses of vitamin E and CoQ₁₀ were tolerated by patients with FRDA for extended periods without any significant adverse effects. All patients showed at least a 2.2-fold increase in serum levels while receiving therapy. While there is some debate as to the effect of increased dietary CoQ₁₀ and vitamin E on tissue levels of these chemicals,¹⁰,¹¹ the observation that they have influenced heart and skeletal muscle ⁳¹P MRS features implies they are at least effectively targeting these tissues.

A decreased energy supply appears to be an important early event in FRDA.¹² The improved cardiac and skeletal muscle MRS data clearly demonstrated that this therapy caused a sustained improvement in this feature of the disease in these tissues. The presence of LVH did not influence the degree of cardiac ⁳¹P MRS improvement in agreement with the suggestion that the energetic defect was not secondary to the hypertrophy. Knowledge about the natural history of cardiac hypertrophy in FRDA is limited and, therefore, it is impossible to identify whether the therapy prevented the progression of hypertrophy.

**Figure 2.** Influence of combined therapy of coenzyme Q₁₀ and vitamin E on echocardiographic data. Intraventricular septal (IVS₆₀) wall thickness in diastole (A), posterior wall thickness in diastole (PW₆₀) (B), and fractional shortening (C). Values are expressed as mean ± SE, n=10. Statistical analyses were performed relative to baseline values using 2-tailed, paired t test. Asterisk indicates P<.05.

**Figure 3.** Influence of combined therapy of coenzyme Q₁₀ and vitamin E on clinical scores. International Co-operative Ataxia Rating Scale (ICARS) score (A), posture and gait score (B), and kinetic score (C). Values are expressed as mean ± SE, n=10. Statistical analyses were performed relative to baseline values using 2-tailed, paired t test. Asterisk indicates P<.05; dagger, P<.01.
While this therapy was not expected to influence the symptoms associated with neuronal loss, we proposed that clinical benefit may be evident if the therapy had a beneficial effect on the function of the remaining cells. Analyzing the patients as a group over the 47 months of therapy demonstrated that the total ICARS score was stable, and the kinetic score tended to improve slightly while the posture and gait score deteriorated. Given the heterogeneity of FRDA with respect to clinical features, genetic severity, and clinical progression rate, the efficacy of any therapy is difficult to interpret if these variables are not considered. Furthermore, the natural history of the clinical symptoms in FRDA is poorly documented, making these assessments difficult to interpret. However, using cross-sectional ICARS data we have attempted to predict the natural history of FRDA with respect to the size of the genetic abnormality (GAA1). We have been able to demonstrate that the clinical progression (total ICARS score) during the 47 months of therapy was better than predicted in 6 patients, and that the kinetic symptoms were improved in 7 patients. However, the posture and gait symptoms continued to decline.

The lack of apparent benefit of combined CoQ10 and idebenone therapy may be related to the improvements in bioenergetics clearly demonstrating its biochemical efficacy. Heart function assessed by fraction shortening significantly improved after 35 and 47 months and, when compared with cross-sectional data, the ICARS and kinetic clinical scores were improved in 7 of 10 patients. However, the posture and gait scores and hand dexterity scores continued to deteriorate. With limited patient numbers and in the absence of a placebo group, these results must be interpreted with caution, and the analysis of therapeutic trials requires improved longitudinal data for a better understanding of the variability of the natural history of the disease. A larger randomized trial focusing on the response to such a therapy of both neurological and cardiological symptoms is required to confirm whether an early diagnosis of FRDA can be exploited to initiate antioxidant treatment and prevent the progression of this disorder.

### Conclusion

This combined therapy CoQ10 and vitamin E caused a prolonged improvement in cardiac and skeletal muscle bioenergetics clearly demonstrating its biochemical efficacy. While this therapy was not expected to influence the symptoms associated with neuronal loss, we proposed that clinical benefit may be evident if the therapy had a beneficial effect on the function of the remaining cells. Analyzing the patients as a group over the 47 months of therapy demonstrated that the total ICARS score was stable, and the kinetic score tended to improve slightly while the posture and gait score deteriorated. Given the heterogeneity of FRDA with respect to clinical features, genetic severity, and clinical progression rate, the efficacy of any therapy is difficult to interpret if these variables are not considered. Furthermore, the natural history of the clinical symptoms in FRDA is poorly documented, making these assessments difficult to interpret. However, using cross-sectional ICARS data we have attempted to predict the natural history of FRDA with respect to the size of the genetic abnormality (GAA1). We have been able to demonstrate that the clinical progression (total ICARS score) during the 47 months of therapy was better than predicted in 6 patients, and that the kinetic symptoms were improved in 7 patients. However, the posture and gait symptoms continued to decline.

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REFERENCES


