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Tolerance of high-dose (3,000 mg/day) coenzyme Q10 in ALS

Abstract—An open-label dose-escalation trial was performed to assess the safety and tolerability of high doses of coenzyme Q10 (CoQ10) in ALS. CoQ10, a cofactor in mitochondrial electron transfer, may improve the mitochondrial dysfunction in ALS. In this study, CoQ10 was safe and well tolerated in 31 subjects treated with doses as high as 3,000 mg/day for 8 months.

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Mitochondrial dysfunction may contribute to neuronal cell death in ALS.¹ Coenzyme Q10 (CoQ10), a free radical scavenger and cofactor in the mitochondrial electron transport chain, is lipophilic and crosses the blood-brain barrier.² CoQ10 is neuroprotective in animal models of ALS and other neurodegenerative disorders.^{3,4} Early-phase trial results of CoQ10 in Huntington disease (HD) and Parkinson disease (PD) suggest that doses greater than 600 mg/day may be needed.^{3,4} The long-term safety of CoQ10 at doses greater than 600 mg/day is not known. For these reasons, we conducted a trial to assess the safety and tolerability of high doses of CoQ10 in ALS.

Methods. *Study design.* This was an open-label dose-escalation safety and tolerability study conducted at four centers

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(IND#66569). Drug was dispensed as wafers containing 600 mg of CoQ10 and 300 IU of vitamin E (Vitaline Formulas, Wilsonville, OR). Vitamin E is added to possibly improve absorption.⁵ Subjects received an escalating dose over 3 months. The subjects took one wafer BID from baseline to month 1, one wafer TID from months 1 to 2, and one wafer QID from months 2 to 3. At month 3, subjects took one wafer five times per day through month 8.

Patient selection criteria. Thirty-one subjects enrolled in the trial. Eligible subjects had a clinical diagnosis of ALS,⁶ a vital capacity (VC) greater than 50% predicted, and symptom onset less than 5 years. Subjects were allowed to take CoQ10 up to their baseline visit.

Procedures. Study procedures included signing informed consent, assessment of eligibility criteria, medical history and examination, VC testing, safety blood tests (complete blood count, electrolytes, glucose, blood urea nitrogen, creatinine, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, total bilirubin, and creatine phosphokinase), urinalysis, muscle testing (maximal voluntary isometric contraction), vital signs and administration of the ALS functional rating scale (ALSFRS-R). Blood samples for CoQ10 plasma levels were obtained monthly prior to dose escalation. Plasma was stored at -80°C and batch shipped frozen for analysis (Dr. Beal) using high-performance liquid chromatography with electrochemical detection.⁷

Safety assessments and statistical analysis. Tolerability was defined as the ability to complete the trial on the maximal dose of CoQ10 without a dose reduction or suspension and was assessed using binomial 90% upper confidence bounds. Safety was assessed by laboratory tests, physical examination findings, vital signs, and adverse events (AEs). As an additional measure of safety, time to first AEs in this trial was compared to that in the placebo cohort from a prior clinical trial of topiramate in ALS using log-rank tests.⁸ For consistency, the placebo data were truncated at 10-month follow-up. The Cox model with forward selection was used to adjust this comparison for baseline characteristics. Survival was compared in a similar way.

The rates of change in MVIC, VC, and ALSFRS-R were considered safety measures and were compared to the placebo cohort. The rates of decline were compared using mixed-effects models to adjust for repeated observations on the same individuals and to control for selected baseline variables. Distributions of baseline characteristics were compared using Fisher's exact tests and *t* tests. The relationship of CoQ10 plasma level with dose over visits was evaluated with mixed-effects models. The AE rates between different doses over the medication time were compared using the Poisson model. With 30 treated patients, we have a 79% chance of seeing at least one occurrence of any toxicity if the true toxicity rate is 5%. The protocol allowed for replacement of subjects who withdrew from the study during the first 2 months of the trial for reasons other than a treatment-related AE.

Results. *Enrollment and baseline demographics.* Thirty-five patients were screened with 31 subjects enrolled. Three subjects did not meet VC criteria and one subject was not on

Table 1 Baseline characteristics

Male participants, %	51.6
Mean age, y	53.7
Mean symptom onset to diagnosis, y	1.0
Mean symptom onset to screening, y	2.0
Entry maximal percentage of vital capacity	86
Riluzole use, %	70
Limb onset, %	84
El Escorial criteria	
No. of definite	23
No. of possible	1
No. of probable	5
No. of laboratory-supported probable	2

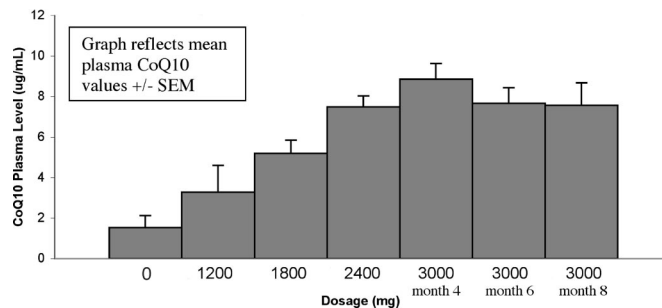
a stable riluzole dose. None of the baseline characteristics were different from the placebo comparison cohort (table 1).

Tolerability. Twenty-five subjects (81%) completed the study on drug. AEs were the reason for study drug discontinuation in four of the six subjects who stopped drug early (see table E-1 on the *Neurology* Web site at www.neurology.org). The other two participants stopped drug early to enter another trial and due to travel difficulties. Twenty-four subjects (77%) completed the study on the maximal dose of 3,000 mg/day. Twenty-nine subjects (94%) reached the maximal dose. One subject reduced study drug (from 3,000 to 2,400 mg/day) during the course of the trial due to abdominal cramping. The subject completed the trial at the reduced dose. There were two dose suspensions and rechallenges. One was due to a myocardial infarction at 3,000 mg/day. The other was due to nausea/indigestion at 600 mg/day. Both subjects completed the study at 3,000 mg/day. The median maximal tolerated dose was 3,000 mg/day.

Safety assessments. There were no significant changes in vital signs or laboratory abnormalities. The most frequent AEs are listed in table 2. AEs were not more frequent at 3,000 mg/day. There was no significant difference in the frequency of AEs when compared to the placebo comparison cohort. Time to the first AE in the CoQ10 group was greater than that of the placebo comparison

Table 2 Most frequent adverse events

Adverse event	No.	%
Headache	5	16.1
Peripheral edema	5	16.1
Rash	5	16.1
Urinary tract infection	5	16.1
Abdominal pain	4	12.9
Constipation	4	12.9
Diarrhea	4	12.9
Arthralgia	4	12.9
Infection	4	12.9
Nausea	3	9.7
Hypertension	3	9.7

**Figure.** Coenzyme Q10 plasma levels by dose.

cohort ($p = 0.002$, hazard ratio [HR] = 0.48). Four of the nine serious AEs during the trial occurred while subjects were on study medication. All reported serious AEs were rated “unlikely” related to study drug by the respective site investigators (see table E-2 on the *Neurology* Web site at www.neurology.org). There was no difference in the rate of change in MVIC arm and grip strength when compared to the placebo cohort. The percentage of CoQ10 subjects alive 10 months after trial initiation was not different from the percentage of subjects in the placebo cohort ($p = 0.12$, HR = 0.40).

Plasma levels and study compliance. Study drug compliance was 98%. Plasma levels of CoQ10 at all doses except 1,200 mg/day were significantly different from the screening value. There was no statistical difference between the levels at 2,400 and 3,000 mg/day (figure). Subjects who took CoQ10 until their baseline visit had higher baseline plasma levels of CoQ10 than participants not taking CoQ10 prior to enrollment ($p = 0.002$).

Discussion. Doses as high as 3,000 mg/day of CoQ10 are safe and well tolerated for as long as 8 months in ALS. This is similar to data published in subjects with PD.⁹ The most common side effects were gastrointestinal. Because dose escalation occurred within subject, we cannot separate out AEs secondary to dose from those due to prolonged drug exposure or disease progression. We chose to dose escalate within subjects to have a larger number of research participants at each dose and because of the possibility that tolerability would be improved with a slower dose escalation within subject. While allowing subjects to take CoQ10 until their baseline visit may have influenced their ability to tolerate the drug, no participant was on doses higher than 1,200 mg/day prior to study enrollment.

The optimal dose of CoQ10 for neurodegenerative disorders is not yet known. While plasma CoQ10 levels increased with each dose escalation in this study, there was no statistical difference in plasma levels between the 2,400 and the 3,000 mg/day groups.

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