MitoQ for Fatigue in Multiple Sclerosis: A Placebo Controlled Trial

NCT04267926

September 23, 2021

Title
MitoQ for fatigue in multiple sclerosis: a placebo-controlled trial

Specific Aims/Purpose
Specific Aim 1: Determine whether Veteran's with MS (VwMS) who receive oral MitoQ in comparison to those who receive placebo have less fatigue after a 12-week treatment period as measured by MFIS Score.
Specific Aim 2: Determine whether VwMS who receive oral MitoQ in comparison to those who receive placebo have improved cognitive function, quality of life and depression using Symbol Digit Modality Test (SDMT), MS Impact Scale -29 (MSIS-29) and the Beck Depression Inventory–Fast Screen scores respectively.
Specific Aim 3: Determine the safety and tolerability of MitoQ in VwMS using side effects and blood tests.
Specific Aim 4: Determine whether plasma MitoQ levels in VwMS treated with MitoQ correlate with clinical outcomes of fatigue, cognitive function, quality of life and depression and with blood based inflammatory immune and oxidative stress biomarkers.
The proposed work is innovative; the

Hypothesis: The central hypothesis is that oral MitoQ with its mitochondrial affinity will improve MS related fatigue, cognition, quality of life and mood by improving mitochondrial function and resultant neuronal energy depletion in neurons.

Research Design and Methods
We propose to conduct a double-blind, placebo-controlled, pilot trial to compare the administration of a 20 and 40 mg dose of oral MitoQ to a placebo, as a treatment to reduce fatigue in MS subjects. There is no research to guide the study supplement dosage for this study. We have chosen 20 and 40 mg dosages based on correspondence from the manufacturer as noted above, in addition to the published recommendation in an article reviewing all the human and animal studies on MitoQ. The participation period for each subject will be 13 weeks: screening visit during the first week, followed by a 12-week treatment period. The study will require 4 visits and 4 phone calls over 13 weeks. Total time commitment is approximately 7 hours.

Overall Design

Aims	Outcomes	Description
1. Determine whether Veterans with MS who receive oral MitoQ in comparison to those who receive placebo have less fatigue after a 12-week treatment period as measured by MFIS Score.	Primary Outcome: MFIS Secondary Outcome: FSS	Double-Blind, randomized groups assigned to either 20 or 40 mg of MitoQ or an identical placebo. Check MFIS, and FSS and SDMT at time 0, 6 and 12 wks
2. Determine whether Veterans with MS who receive oral MitoQ in comparison to those who receive placebo, have improved cognitive function, quality of life and depression using SDMT, MSIS-29 and the BDI–FS scores respectively.	Secondary Outcome: SA-EDSS and BDI.	Double-Blind, randomized groups assigned to either 20 or 40 mg of MitoQ or an identical placebo. Check SA-EDSS and BDI at time 0 and 12 weeks
3. Determine the safety and tolerability of MitoQ in subjects with MS using side effects and blood tests.	Secondary Outcome: Safety.	Monitoring of patient response and reporting/recording AEs
4. Determine whether plasma MitoQ levels in Veterans with MS treated with MitoQ correlate with clinical outcomes of fatigue, cognitive function, quality of life, depression, blood inflammatory immune markers, and markers of oxidative stress.	Secondary Outcome: Plasma levels of oral MitoQ 1 hr post-drug. Plasma and/or PBMC IFN-γ, TNF-α, IL-2, IL-6 and IL-17, MDA, HAE, TAC, NOC and SOD	Data collection on MitoQ plasma levels and inflammatory and oxidative stress markers at baseline, week 6 and 12.

Subject Visits and Assessment Schedule

Table 2. Study Activities	**Week 0**	**Week 1**	**Week 7**	**Week 13**	
	Visit 1	Visit 2	Visit 3	Visit 4	
Visit time	2 hours	2.5 hours	2.5 hours	2.5 hours	
Purpose	screen, consent	begin treatment	in clinic follow up	end treatment	Total blood draw amount
Consent	X				
Vital signs	X	X	X	X	
Medical history, physical neurological exam	X			X	
T25W, 9HPT, SDMT		X	X	X	
BDI, FSS, MFIS, MSIS-29	X	X	X	X	
Blood testing CBC w/ diff (4mls) CMP (6mls)	X		X	X	30 mls
Blood draw for plasma MitoQ level (4mls)		X	X	X	12 mls
Blood draw for Inflammatory immune markers 40 mls		X	X	X	120 mls
Medication reconciliation	X	X	X	X	
Urine testing (female)	X		X	X	
Side effect monitoring			X	X	

Specific Aim 1: Determine whether Veterans with MS who receive oral MitoQ in comparison to those who receive placebo have less fatigue after a 12-week treatment period as measured by MFIS Score. Our hypothesis is that MitoQ preserves or improves the mitochondrial function and that in turn may improve fatigue in MS therefore MS veterans taking MitoQ will have less fatigue than those Veterans with MS taking placebo.

Introduction: Fatigue, a common MS symptom can be a cause of significant disability, and loss in quality of life in Veterans with MS. While the mechanisms responsible for fatigue in MS are poorly understood it is possible that reversible mitochondrial dysfunction due to oxidative stress and resultant neuronal ATP depletion may contribute to fatigue. Orally administered MitoQ is a mitochondria-targeted antioxidant similar to CoQ10 but more effective in migration to mitochondria compared to CoQ10 and is aimed at reducing the effects of mitochondria-derived ROS, which lead to mitochondrial dysfunction. While a pilot study using CoQ10 for fatigue improvement in MS showed positive results, studies evaluating effects of oral MitoQ in MS have not been conducted.

Procedures: We will determine the effects of 20 or 40 mg oral MitoQ versus placebo on MS fatigue as measured by MFIS. We will obtain descriptive information about changes in MFIS scores for each subject group and will use the collected data to determine the mean, SD, and confidence interval of this change. This information will also help determine sample size and power analysis for a future phase II trial. This study will be the first to assess whether MitoQ changes fatigue in MS subjects. Data from MFIS scores taken at baseline assessment, and 6- and 12-week time points will be assessed, to determine changes in MFIS fatigue scores. The primary outcome measure will be the change from baseline total MFIS score to 12-week total MFIS score. Secondary outcome measures will be the change from baseline to each of the following measures: 6-week MFIS and 6 and 12-week FSS scores.

Statistical Analysis

Data Analysis: We will obtain descriptive information on primary and secondary outcomes. In particular, at each time-point, we will obtain the mean, median, SD, and range for each measure and for the changes from baseline for each measure, for the MitoQ and placebo subject groups. We will also obtain 95% confidence intervals for the changes from baseline for each measure, at each time point for both subject groups. We will conduct a t-test to compare primary and secondary measures (changes from baseline) and to obtain the associated 95% confidence intervals for the differences in mean change between the MitoQ and placebo subject groups. We will focus on the confidence intervals that describe the plausible differences in mean change between the subject groups. These confidence intervals will provide information about the magnitude of differences in MFIS and FSS changes between subject groups that are consistent with the previous data. We will also test for differences in the change scores by group in a linear regression framework, adjusting for demographic and clinical characteristics, such as gender. As a secondary analysis, we will use an ANCOVA test with 12-week MFIS score as the outcome and baseline MFIS score as a covariate to account for baseline differences in fatigue among patients. We will use a linear mixed model to analyze MFIS changes over time with fixed effects for time, incorporating baseline values of the outcome as a covariate, and random intercepts and slopes for individuals to incorporate within-subject variability. Due to the exploratory nature of this study, the 6 week time point will provide evidence of whether or not change is seen by 6 weeks. It will allow us to understand how long MitoQ takes to have an effect, and this information will be useful for planning future studies. Both formal hypothesis testing and confidence interval estimation will be conducted. To detect a trend in the effect of MitoQ dosage, we will perform an ANOVA trend analysis on the change in MFIS between baseline and 12 weeks among the three treatment groups. In addition, we will categorize participants who improved by a reliable change, defined as differences in group means divided by the standard error, greater than 1.96 points and test for differences in the proportion of improvers by group using a chi–squared test. The standard error is given by $s_1\sqrt{1-r_{xx}}$, where s_1 is the standard deviation of the control group and r_{xx} is the MFIS test-retest reliability (here, given by the MFIS Cronbach's alpha value of 0.81.[6] This analysis will yield additional power (compared to a 2-sample t-test) and will provide useful data for planning a repeated measures analysis in a future larger trial. Secondary outcomes will be analyzed in the same manner. To test if the effect of MitoQ on FSS depended on compliance, compliance (as measured by pill counting) will be treated as a co-variate in the analyses. Patterns of missing data will be examined to determine if patient characteristics are related to missing follow-up data. Statistical significance is defined as $P < 0.05$. SPSS for Windows Version 15.0 (SPSS Inc., Chicago) and SAS (SAS Institute, Cary, NC) will be used for analysis.

Anticipated results: We expect that MS veterans taking MitoQ for 12 weeks will have less fatigue than those Veterans with MS taking placebo as determined by the MFIS.

Specific Aim 2: Determine whether Veterans with MS who receive oral MitoQ in comparison to those who receive placebo have improved cognitive function, quality of life and depression using Symbol Digit Modality Test (SDMT), MS Impact Scale -29 (MSIS-29) and the Beck Depression Inventory–Fast Screen scores respectively.

Our hypothesis is that by improving mitochondrial function in sub optimally functioning neurons and axons, MitoQ, an efficient mitochondrial targeted therapy, may lead to cognition, quality of life and depression improvement in Veterans with MS.

Introduction: In addition to fatigue, cognitive impairment, poor quality of life and depression are some aspects of MS that have significant adverse impact on patient's lives and not addressed by current treatment options including the disease modifying therapies. Mitochondrial targeted therapy CoQ10 has shown significant improvement in depression (BDI) and quality of life in a small pilot study as compared to placebo.[46] Since MitoQ is considered to have better mitochondrial penetration than CoQ10, it is worthy of exploring its effects on these poorly managed MS symptoms.

Procedures: At baseline assessment and visits 3 and 4 (6 and 12-week post treatment initiation assessment). At each of these visits, we will also acquire data on each subject's cognitive function using SDMT, quality of life assessment using MSIS-29 and depression using BDI-FS scores.

Statistical Analysis: Exploratory analyses similar to the primary analysis including mixed model that will account for repeated measures will be conducted using the SDMT, MSIS-29 and BDI-FS as the secondary outcome measures. To test if the effect of MitoQ depended on changes in depression a similar model will be constructed including both the baseline and the end of the period BDI-FS. The effect of MitoQ on depression will be evaluated by fitting a model with BDI-FS at the end of each period as the outcome. Baseline values for the SDMT, MSIS-

29, BDI-FS and FSS will be included as covariates, and patient effects treated as random. Changes in activity over time will be analyzed in an exploratory manner using graphical techniques.
Anticipated results: We expect that MS veterans taking MitoQ will have better cognition and quality of life and less depression than those Veterans with MS taking placebo as determined by the standard measures.

Specific Aim 3: Determine the safety and tolerability of MitoQ in subjects with MS using side effects and blood tests.
Introduction: Results from clinical trials in Hepatitis C and PD as described in the "current status of the field section" suggested that MitoQ is generally well-tolerated and no safety concerns surfaced. To assess the safety and tolerability of oral MitoQ versus a placebo, all subjects (treatment as well as the placebo groups) will undergo monitoring for AEs and side-effects as described below. An adverse event is any untoward medical occurrence (signs, symptoms, intercurrent illness or abnormal lab findings) that occurs in a study subject during the treatment or cross over periods, regardless of suspected cause.
Statistical Analysis: To evaluate patient safety, laboratory test results at baseline and changes from baseline at 6 and 12 weeks will be determined and summarized for each subject group, and will be compared using t-tests for continuous measures and Fisher's exact test for proportions.
Anticipated results: We expect that MS veterans taking MitoQ will have no significant and unexpected AE on their blood tests and body systems than those Veterans with MS taking placebo.

Specific Aim 4: Determine whether plasma MitoQ levels in Veterans with MS treated with MitoQ correlate with clinical outcomes of fatigue, cognitive function, quality of life, depression, blood inflammatory immune markers, and markers of oxidative stress. We will test the hypothesis that plasma concentrations of MitoQ correlate with fatigue, cognitive function, quality of life and depression in subjects with MS receiving MitoQ compared with those receiving placebo. Additionally, this aim will test the hypothesis that MitoQ will lower the blood concentration of inflammatory immune markers and markers of oxidative stress. We hypothesize that MS subjects receiving MitoQ will have improved levels of blood biomarkers of oxidative stress as seen by lower lipid peroxidation (LPO) products, nitric oxide catabolites (NOC) and superoxide dismutase (SOD) activity and improved TAC.
Introduction: Pharmacokinetic (PK) studies of oral MitoQ have been conducted in healthy human subjects but not in MS. Healthy human PK studies suggest maximal plasma concentration (Cmax) of MitoQ after oral dosing at 40 mg (0.5 mg/kg) and 20 mg (0.25 mg/kg) to have detectable and maximal concentration ~1hr. Limited CoQ10 studies in MS suggest significant impact on cytokine and oxidative stress biomarker profile hence we believe that MitoQ may have similar effects too. We now have good in vitro data on the ability of MitoQ to suppress LPS-induced cytokine production in human peripheral blood mononuclear cells and this study will provide a novel opportunity to explore the biologic effects of MitoQ. With the data collected on clinical outcomes such as fatigue, cognition, depression and QOL in this study, we will be able to generate pilot data correlating the PK, immune markers and these clinical outcomes.
Statistical analysis. We will construct Q-Q plots on all data to test for normalcy. Using Pearson correlations for parametric data or Spearman Rho correlations for nonparametric data, we will determine linear associations among changes in cytokines including IFN-γ, TNF-α, and IL-2 and plasma levels of MitoQ. We will use repeated measures mixed effects models to investigate the linear relationships between pro-inflammatory markers, oxidative stress biomarkers, cytokines, and MitoQ levels over time (i.e., at 6 and 12 weeks). We will examine correlation between measures of oxidative stress as well as the correlation between oxidative stress markers and plasma levels of MitoQ. We will obtain mean changes from baseline to 12 weeks and 95% confidence intervals for the oxidative stress markers. The correlations, means, and standard deviations observed in the oxidative stress biomarkers of this study will help inform power and sample size calculations in future trials. Statistical significance is defined as $P < 0.05$.
Anticipated results: We expect that plasma concentrations of MitoQ will correlate with fatigue, cognitive function, quality of life and depression in subjects with MS and that subjects receiving MitoQ will have lower blood concentration of inflammatory and oxidative stress markers.