Journal of Clinical Lipidology (2013) 7, 187–193

Journal of Clinical Lipidology

Original Articles

A randomized trial of coenzyme Q10 in patients with statin myopathy: Rationale and study design

Beth A. Parker, PhD, Sara M. Gregory, PhD*, Lindsay Lorson, BS, Donna Polk, MD, C. Michael White, PharmD, Paul D. Thompson, MD

Division of Cardiology, Henry Low Heart Center, 80 Seymour Street, Hartford Hospital, Hartford, CT 06102, USA

KEYWORDS:
Muscle pain;
Myalgia;
Physical performance;
Simvastatin;
Strength;
Ubiquinone

BACKGROUND: Statins are the most commonly prescribed and effective medications for reducing low-density lipoprotein levels. Some patients experience myopathic symptoms during statin treatment. The etiology is not known, but depletion of mevalonate pathway metabolites, including coenzyme Q10 (CoQ10), has been suggested. Despite a lack of conclusive evidence supporting its utility, CoQ10 supplementation has been recommended to patients who experience myalgic symptoms.

OBJECTIVE: The Co-Enzyme Q10 in Statin Myopathy study is designed to examine the effect of CoQ10 supplementation on the extent and intensity of muscle pain during treatment with simvastatin.

METHODS: We will recruit patients with a documented history of myalgia during statin treatment. The presence of statin-related myalgia will be confirmed in a crossover run-in trial during which the presence and absence of symptoms will be documented during statin and placebo treatment, respectively. Individuals experience myalgic symptoms while taking statins but not placebo will be randomized to receive simvastatin 20 mg daily plus either 600 mg daily of CoQ10 or placebo. Muscle pain intensity will be documented during weekly phone calls via use of the Brief Pain Inventory, Short Form. Treatment will continue for 8 weeks or until muscle symptoms are reported continuously for 1 week or become intolerable, and then subjects will crossover to the alternative treatment (CoQ10 or placebo).

RESULTS: This study is an ongoing clinical trial.

CONCLUSIONS: This study will determine the utility of CoQ10 for reducing pain intensity in myalgic patients and will provide guidance for clinicians treating patients with hypercholesterolemia who are intolerant to statins.

Hydroxy-methylglutaryl-coenzyme A reductase inhibitors or statins are widely prescribed to reduce low-density lipoprotein (LDL) cholesterol concentrations and can reduce cardiac events by 20%–35%.[1] Recommendations by the National Cholesterol Education Program Adult Treatment Panel III advocate more aggressive management of LDL cholesterol levels (<70 mg/dL in high-risk patients), which means that statin medications will be prescribed more frequently and in greater doses.[2] Statins are generally well-tolerated, but some patients complain of muscular symptoms, including myalgia, muscle cramps, weakness, and in rare circumstances life-threatening rhabdomyolysis.[3] The reported incidence of myalgic symptoms with statin treatment ranges from 1%[3] to 25%,[4] and muscular complaints may compromise patient compliance.[3]

How statins produce muscular side effects is not clear, but depletion of ubiquinone or coenzyme Q10 (CoQ10), which is also produced by the cholesterol metabolic pathway, has been suggested as the mechanism

* Corresponding author.
E-mail address: sgregory@harthosp.org

Submitted January 2, 2013. Accepted for publication February 18, 2013.

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http://dx.doi.org/10.1016/j.jacl.2013.02.002

(Fig. 1).[5] Consequently, CoQ10 supplementation is used by many patients and prescribers of statins despite ambiguous study results. CoQ10 blood levels decrease during statin treatment, but CoQ10 is carried in the LDL, so most investigators have attributed this decrease to decreases in low-density and very-low-density lipoproteins.[5]

Studies of muscle biopsies have not demonstrated consistent reductions in intramuscular CoQ10 during statin therapy,[5] although intramuscular CoQ10 levels were reduced by approximately 30% in subjects with microscopic muscle damage during treatment with 80 mg of simvastatin,[6] and intramuscular CoQ10 levels were reduced 2–4 standard deviations below normal in approximately 50% of patients with statin myopathy (Vladitu et al, unpublished work presented at the American College of Rheumatology 2004 Annual Meeting). Thus, intramuscular depletion of CoQ10 may be a viable explanation for statin myopathy.

CoQ10 supplementation and its effects on statin myalgia have not been extensively studied, and results from supplementation trials vary. Treatment with 100 mg/day of CoQ10 reduced pain severity and pain interference with daily activities during statin treatment in patients with a history of myalgia.[7] In contrast, 200 mg/day of CoQ10 did not affect myalgia score, compliance with statin treatment, or the number of patients tolerating high-dose simvastatin therapy during upward dose titration of simvastatin from 10 to 40 mg/day.[8] The research supporting CoQ10 supplementation during statin treatment is therefore ambiguous, but CoQ10 supplementation is used by many patients and prescribers of statins despite these ambiguous study results. The efficacy of CoQ10 supplementation needs to be verified so that patients with statin intolerance and clinicians can make appropriate recommendations on the potential benefit of this popular supplement.

The Co-Enzyme Q10 in Statin Myopathy study (NCT01140308) will examine the utility of CoQ10 supplementation by testing the hypothesis that supplementation will reduce the intensity of pain during statin treatment compared with the use of placebo in patients with a documented history of statin myalgia. The time to onset of myalgia, as well as effects on objective measures of physical performance will be assessed.

Methods

Study overview

The study is designed to ensure that the CoQ10 section of the study treats only subjects with documented statin myalgia. Consequently, we will recruit patients with a history of myopathic complaints during statin treatment from the Cholesterol Management Center at Hartford Hospital, newspaper and radio advertisements, and contact with physicians' offices. Recruited subjects will undergo a run-in crossover trial to confirm statin-associated myalgia. Only subjects who develop myalgic symptoms during treatment with simvastatin, but not placebo, will then participate in the CoQ10 treatment section of the study to determine whether supplementation reduces muscle pain in patients with documented statin myalgia (Fig. 2).

Run-in trial to confirm myalgia

After 4 weeks off statin treatment, recruited subjects will be treated with either 20 mg of simvastatin or placebo daily for 8 weeks or until muscle symptoms persist for 1 week or are intolerable. Muscle symptoms will be documented weekly. After a 4-week wash-out period, subjects will crossover to the alternative treatment (simvastatin 20 mg or placebo). Only subjects who experience new muscle pain on simvastatin but *not* on placebo that resolves within 4 weeks off treatment will be entered into the CoQ10 section of the study.

CoQ10 treatment study

After a 4-week wash-out period after the run-in trial, subjects qualifying for the CoQ10 protocol will be randomized into groups treated with 20 mg of simvastatin with either 600 mg of CoQ10 or placebo for 8 weeks until muscle symptoms are experienced continuously for 1 week or until symptoms are intolerable. We selected an 8-week treatment period for both the run-in and treatment study because in the largest clinical trial the median time to onset of symptoms was 1 month,[9] and symptoms are typically provoked sooner with statin rechallenge.[3] After 4 weeks off treatment, subjects will cross over to the alternative group: statin/CoQ10 or statin/placebo. Subjects will be first loaded for 2 weeks with either CoQ10 or placebo to ensure adequate tissue levels before beginning simvastatin treatment. Pain intensity will be recorded weekly, and subjects will undergo additional testing, including a blood draw, muscle performance and exercise capacity, physical activity level monitoring, and a pain questionnaire at the beginning and end of each treatment phase.

Study monitoring

The Coenzyme Q10 in Statin Myopathy study is approved by the Institutional Review Board at Hartford Hospital. A Data Safety and Monitoring Board (DSMB) composed of two physicians and a statistician will oversee the project with biannual meetings. The purpose of the DSMB is to conduct periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcomes. In addition, significant adverse event reports as well as safety data (creatine kinase [CK] and alanine aminotransaminase values) will be provided to the DSMB at each meeting. Members will discuss and analyze these data to determine whether the trial should be stopped. Stopping rules are as follows: (1) The presence of a significantly greater frequency of adverse events related to the drug, and (2) the emergence of unexpected serious adverse experience(s) not