

Treatment of statin adverse effects with supplemental Coenzyme Q₁₀ and statin drug discontinuation

Peter H. Langsjoen^{a,*}, Jens O. Langsjoen^b, Alena M. Langsjoen^c and Lindsay A. Lucas^d

^a*East Texas Medical Center and Trinity Mother Francis Hospital, Tyler, TX, USA*

^b*University of Texas Medical Branch, Galveston, TX, USA*

^c*Coenzyme Q₁₀ Laboratory, Inc., Tyler, TX, USA*

^d*Hollins University, Roanoke, VA, USA*

Abstract. Fifty consecutive new cardiology clinic patients who were on statin drug therapy (for an average of 28 months) on their initial visit were evaluated for possible adverse statin effects (myalgia, fatigue, dyspnea, memory loss, and peripheral neuropathy). All patients discontinued statin therapy due to side effects and began supplemental CoQ₁₀ at an average of 240 mg/day upon initial visit. Patients have been followed for an average of 22 months with 84% of the patients followed now for more than 12 months. The prevalence of patient symptoms on initial visit and on most recent follow-up demonstrated a decrease in fatigue from 84% to 16%, myalgia from 64% to 6%, dyspnea from 58% to 12%, memory loss from 8% to 4% and peripheral neuropathy from 10% to 2%. There were two deaths from lung cancer and one death from aortic stenosis with no strokes or myocardial infarctions. Measurements of heart function either improved or remained stable in the majority of patients. We conclude that statin-related side effects, including statin cardiomyopathy, are far more common than previously published and are reversible with the combination of statin discontinuation and supplemental CoQ₁₀. We saw no adverse consequences from statin discontinuation.

Keywords: Statin cardiomyopathy, coenzyme Q₁₀, CoQ₁₀, ubiquinone, statins, statin side effects, HMG-CoA reductase inhibitors

1. Introduction

The practice of medicine is increasingly influenced by aggressive cholesterol reduction through the use of ever increasing dosages and potencies of HMG-CoA reductase inhibitors (statins). Statin drugs represent a class of cholesterol-lowering medications of remarkable profitability and popularity that have changed the practice of medicine with ever-changing guidelines that have become increasingly onerous on both patients and physicians alike, with increasing financial and physical burdens. It is becoming clear to practicing physicians that this struggle to obtain an ever lower cholesterol level is accompanied by a substantial decline in quality of life, which limits patient compliance with drug therapy and strains physician-patient relationships. It is the purpose of this study to evaluate the clinical status of statin-treated patients, and importantly, to evaluate what happens when statin drug therapy is withdrawn in the face of adverse statin effects.

* Address for correspondence: Peter H. Langsjoen, MD, FACC, 1107 Doctors Dr., Tyler, TX 75701, USA. E-mail: langsjoen@compuserve.com.

2. Background

It is well recognized that the inhibition by HMG-CoA reductase inhibitors of mevalonate synthesis blocks both the biosynthesis of cholesterol and the biosynthesis of the vitamin-like nutrient coenzyme Q₁₀ (CoQ₁₀ or ubiquinone). CoQ₁₀ is well established to be an essential component in mitochondrial ATP production as well as in several other aspects of cellular metabolism. Reduced CoQ₁₀ (ubiquinol) is recognized to be a clinically relevant antioxidant. The metabolism and functions of CoQ₁₀ have recently been reviewed and very well referenced [9]. It is clear that the higher the dosage of any particular statin drug and the higher the potency of individual statin drug, the greater will be the reduction of coenzyme Q₁₀. The new cholesterol lowering guidelines have brought about much more significant depletion in coenzyme Q₁₀. There are substantial animal and human studies that document this drug nutrient interaction which has been reviewed [1,4,5]. Significant reductions in both plasma and skeletal muscle CoQ₁₀ levels along with impaired mitochondrial respiratory chain enzyme activities have recently been observed in patients on 80 mg/day of simvastatin [6]. There is evidence that supplemental coenzyme Q₁₀ can reverse statin drug-induced myalgia [3] as well as reverse statin drug induced heart muscle weakness in the form of diastolic dysfunction [8]. For these reasons we chose to supplement all 50 of our patients who were experiencing one or more statin drug side effects with an average of 240 mg of coenzyme Q₁₀ per day in addition to discontinuing their statin medication.

3. Methods

A prospective analysis of 328 consecutive new cardiology clinic patients over a two-year period of time between January 2002 and December 2003 identified a subset of 50 patients who were actively taking statin drug therapy at the time of their initial visit. Patients were excluded if they were being seen as a one-time consultation and therefore would not be available for follow-up. Patients who had previously been on statin drug therapy but had stopped the drug prior to their initial visit were also excluded. Furthermore, we excluded patients taking red yeast rice extract even though this over-the-counter product has HMG-CoA reductase inhibitor activity. All patients were evaluated for five possible categories of statin adverse effects: myalgia with or without muscle weakness, fatigue, dyspnea, memory loss and peripheral neuropathy. Realizing that all of these symptoms can have many possible causes, we excluded those symptoms with clear non-statin drug etiologies. For example, peripheral neuropathy was excluded as a possible statin adverse effect in all patients with diabetes mellitus or vitamin B12 deficiency. Further, memory loss was excluded in all patients with the diagnosis of Alzheimer's, Parkinson's or previous stroke. Myalgia, fatigue and dyspnea were much more difficult to sort out and most of these were included as possible statin adverse effects, but all symptoms had to be chief complaints on initial visit.

Echocardiography was performed on initial visit, and on follow-up visits as clinically indicated. All echocardiograms were performed by the same technician on a Toshiba Power Vision with standard measurements of chamber dimensions and left ventricular function. Diastolic function was measured by pulsed wave Doppler of the mitral valve inflow at the leaflet tips from the apical four chamber view. Mitral valve inflow slope (EF slope in m/sec²), and E/A ratio were recorded as indices of diastolic function.

All 50 patients presented with one or more statin-related adverse effects as their chief complaint and therefore their statin drug therapy was discontinued upon initial visit and all patients simultaneously began supplemental coenzyme Q₁₀ at an average dose of 240 mg per day. Because of the well documented

Table 1
Patient statistics

Total number of statin patients	50
Mean Age	66 years
Age Range	44–84 years
Males	58%
Females	42%

Table 2
Patient diagnoses

Diagnoses	total
Diastolic Dysfunction	52%
Idiopathic Dilated Cardiomyopathy	6%
Ischemic Heart Disease	58%
Hypertension	38%
Diabetes Melitus	16%
Emphysema	14%
Congestive Heart Failure	8%
Pericardial Effusion	2%
Valvular Heart Disease	12%
Arrhythmia	22%
Peripheral Vascular Disease	6%

Table 3
Type of statin on initial patient visit

Lipitor (atorvastatin)	52%
Zocor (simvastatin)	34%
Pravachol (pravastatin)	10%
Mevacor (lovastatin)	2%
Lescol (fluvastatin)	2%

coenzyme Q₁₀ depleting effect of statin drug therapy, we chose to supplement all of these symptomatic patients with coenzyme Q₁₀ in order to maximize their recovery [4,5]. Patients were then carefully followed in the clinic for an average of 22.4 months (range of 2 to 41 months) with 84% followed now for more than 12 months, and 51% followed now for more than 24 months. The average number of follow-up visits per patient was six visits (range of 1 to 13 visits). Eight patients who have not been seen for over 12 months are considered to be now lost to follow-up. Twenty-eight out of the 50 patients had both initial and follow-up echocardiograms for analysis.

4. Results

The baseline characteristics of the 50 consecutive patients and their presenting diagnoses are noted in Tables 1 and 2, with the specific type of statin and duration of statin use noted in Tables 3 and 4. The most popular statins were Lipitor at 52% and Zocor at 34% and an average duration of statin use was more than two years (28 months). Patients presented with the usual mix of ischemic heart disease (58%), hypertensive heart disease (38%), diabetes mellitus (16%), and emphysema (14%). A surprisingly high percentage (52%) had diastolic left ventricular dysfunction on initial visit as measured by E/A ratio and EF slope.

The prevalence of possible statin adverse effects on initial visit and on most recent follow-up visit is outlined in Table 5. The majority of patients were quite ill on initial visit with fatigue (84%) and

Table 4
Duration of statin use

Less than 6 months	12%
6 months to less than 1 year	10%
1 year to less than 2 years	2%
2 years to less than 3 years	16%
3 years to less than 4 years	2%
4 years or more	10%
Patient can't remember	49%
Average duration of statin use	28 months

Table 5
Prevalence of symptoms on initial and follow-up visits

Symptom	Prevalence of symptoms on initial visit	Prevalence of symptoms on latest follow-up
Myalgia	64%	6%
Fatigue	84%	16%
Dyspnea	58%	12%
Memory Loss	8%	4%
Peripheral Neuropathy	10%	2%

myalgia (64%) with and without proximal muscle weakness. Two of these patients had mild elevation of serum creatinine kinase and no patient had rhabdomyolysis. Histopathologic muscle damage with normal creatinine kinase levels has been well documented during statin drug therapy by Phillips et al. [7] Patients with dyspnea had either myocardial dysfunction (decreased ejection fraction, diastolic dysfunction, or both) or chronic obstructive pulmonary disease. Memory loss was a significant complaint in 8% of patients and was often accompanied by irritability and personality changes that were commented upon by close family members. Patients with peripheral neuropathy had sensory loss and paresthesias in the lower legs and feet.

There was a strong tendency for the most severe symptoms to be observed in the older patients, and in those with the longest duration of statin use. After the initial visit with the discontinuation of statin drug therapy and the addition of supplemental coenzyme Q₁₀ there was rapid improvement in most symptoms. Fatigue and myalgia were beginning to improve by one month follow-up, and quite significantly improved by three month follow-up. Dyspnea was less predictable, particularly in those patients with chronic obstructive pulmonary disease. Memory loss and peripheral neuropathy improved, more slowly over 6 to 12 months with some patients having major problems with residual symptoms, even after more than one year follow-up. The prevalence of patient symptoms on initial visit and on most recent follow-up demonstrated a decrease in fatigue from 84% to 16%, myalgia from 64% to 6%, dyspnea from 58% to 12%, memory loss from 8% to 4% and peripheral neuropathy from 10% to 2% (Table 5).

Importantly, we saw no evidence of any adverse consequences upon the statin drug discontinuation. With 84% of patients having been followed now for more than one year, we have observed no cases of myocardial infarction or stroke. There have been three deaths, two from lung cancer in smokers, and one from inoperable severe aortic stenosis. Only one patient has undergone coronary artery bypass graft surgery during follow-up. Due to the known beneficial anti-inflammatory properties of statin drugs in patients with ischemic heart disease, we were especially vigilant for any possible clinical deterioration in these patients. We observed no instances of accelerated or unstable angina upon statin drug discontinuation.

Table 6
Echo measurements

	Ejection Fraction (%)	Diastolic Dysfunction		Abnormal LVEDD (starting LVEDD > 6.0 cm)
		(starting EFS < 2.0 m/sec ²)	(starting E/A ratio < 1.0)	
Total number of patients	28	13	16	6
% Improved	50% (8.5 point increase)	46.2% (2.1 m/sec ² increase)	50% (0.2 increase)	50% (0.7 cm decrease)
% Unchanged	35.7%	15.4%	25%	50%
% Worsened	14.3% (7.5 point decrease)	38.5% (1.3 m/sec ² decrease)	25% (0.2 decrease)	0%

Initial and follow-up echocardiograms were available in 28 of the 50 patients with pertinent data on left ventricular size and function noted in Table 6. Left ventricular ejection fraction improved by an average of 8.5 points in 50% of patients, remained the same in 35.7% of patients and worsened in only 14.3%. Thirteen patients had diastolic dysfunction as measured by EF slope of less than 2.0 m/sec² and 16 patients by EA ratio less than 1.0. The majority of patients with diastolic dysfunction either improved or remained stable. Six patients had left ventricular enlargement on initial visit (left ventricular end diastolic dimension more than 6 cm) with three patients decreasing in heart size by an average of 0.7 cm and three patients remained essentially unchanged. Echocardiographic improvements correlated well with clinical improvements. Several patients had impaired left ventricular function with either decreased ejection fraction, diastolic dysfunction, or both, without ischemic, valvular, or hypertensive heart disease and were termed “statin cardiomyopathy”. We believe these cases of statin related heart failure to be the clinical extension of previously published statin induced diastolic dysfunction [8]. In that study of 14 patients with normal baseline left ventricular function, 71% percent developed asymptomatic diastolic dysfunction after only six months of Lipitor at 20 mg per day.

5. Discussion

The weaknesses of our study include the open design, two simultaneous interventions (the discontinuation of statin drug therapy in all patients and the initiation of supplemental coenzyme Q₁₀ in all patients) and the subjective nature of symptoms. The strengths of our study include prospective design, close follow-up and excellent applicability of our findings to the real world of clinical medicine. We believe that a significant impairment in patient quality of life explains the documented poor compliance with statin drug therapy as recently reported by Jackevicius et al. [2]. In this Canadian study of 85,020 patients on statin drug therapy for primary prevention, 75% had discontinued their drug therapy after two years. It is important for patients and physicians alike to realize that statin drug therapy can be safely discontinued in settings of adverse effects and along with supplemental CoQ₁₀ brings about an improvement in quality of life with no clinically apparent aggravation of underlying atherosclerotic disease.

References

- [1] I.P. Hargreaves, A.J. Duncan, S.J.R. Heales and J.M. Land, The effect of HMG-CoA reductase inhibitors on coenzyme Q₁₀, *Drug Safety* **28**(8), 659–676.
- [2] C.A. Jackevicius, M. Mamdani and J.V. Tu, Adherence with statin therapy in elderly patients with and without acute coronary syndromes, *JAMA* **288**(4) (2002), 462–467.
- [3] P. Kelly, Coenzyme Q₁₀ improves myopathic pain in statin-treated patients, *American College of Cardiology 54th Annual Scientific Sessions*, March 6–9, Orlando, Florida (2005), 1001–117 (Abstract).

- [4] P.H. Langsjoen and A.M. Langsjoen, The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q₁₀: A review of animal and human publications, *BioFactors* **18**(1–4) (2003), 101–111.
- [5] P.H. Langsjoen, G.P. Littarru and M.A. Silver, Role of concomitant coenzyme Q₁₀ with statins for patients with hyperlipidemia, *Current Topics in Nutraceutical Research* **3**(3) (2005), 149–158.
- [6] H. Päivä, K.M. Thelen, R. VanCoster, J. Smet, B. De Paepe, K.M. Mattila, J. Laakso, T. Lehtimäki, K von Bergmann, D. Lutjohann and R. Laaksonen. High-dose statins and skeletal muscle metabolism in humans: A randomized, controlled trial, *Clinical Pharmacology Therapeutics* **78** (2005), 60–68.
- [7] P.S. Phillips, R.H. Haas, S. Bannykh, S. Hathaway, N.L. Gray, B.J. Kimura, G.D. Vladutiu and J.D. England. Statin-associated myopathy with normal creatine kinase levels, *Annals of Internal Medicine* **137**(7) (2002), 581–585.
- [8] M.A. Silver, P.H. Langsjoen, S. Szabo, H. Patil and A. Zelinger, Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q₁₀ to reverse that dysfunction, *American Journal of Cardiology* **94** (2004), 1306–1310.
- [9] M. Turunen, J. Olsson and G. Dallner, Metabolism and function of coenzyme Q, *Biochimica et Biophysica Acta* **1660** (2004), 171–199.