

## **Managing statin-related muscle problems**

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*A 60-year-old man with coronary artery disease comes for a follow-up visit. At his previous visit 2 months ago, you reduced his atorvastatin dose to 10 mg from 40 mg daily as he complained of severe myalgia and his creatine kinase level was twice the upper limit of normal. No other cause was found for his muscle problem. After taking the reduced dose for 3 weeks he stopped atorvastatin completely as troublesome myalgia persisted. He has not taken a statin in the last 5 weeks and his myalgia has improved. Now he is reluctant to be restarted on a statin.*

*What are your options to manage this patient?*

### **Introduction**

Based on a large and consistent body of evidence, many patients receive statins on a long term basis for primary and secondary prevention of cardiovascular diseases.

Statin-related muscle disease is the most commonly cited side effect of its use and a clinically important cause of statin intolerance and the need to discontinue. The spectrum of the muscle disease ranges from common but clinically benign myalgia to rare but life-threatening rhabdomyolysis. Clinical trials have reported that 1.5-5% of statin users have myopathy.<sup>1</sup> However; in the practice setting an incidence up to 33% has been reported.<sup>2</sup> The Prediction of Muscular Risk in Observational Conditions (PRIMO) project reported<sup>3</sup> from a cohort of 7924 unselected hyperlipidemic patients in France who received high-dose statin therapy, muscular symptoms in 10.5%. A recent meta-analysis of 90 observational cohort and case-control studies<sup>4</sup> identified an increased risk for myopathy among statin users relative to controls (odds ratio, 2.63; 95% confidence interval, 1.50-4.61). It is difficult to directly compare the incidence of statin myopathy in clinical trials with real world clinical practice given the inconsistent definitions. Clinical trials define myopathy only when the creatine kinase (CK) level is greater than 10 times the normal upper limit, in keeping with the FDA definition.<sup>1</sup> The differences might also be related to the systematic exclusion of individuals with a history of statin intolerance from clinical trials and the individuals withholding consent for trials if they have previously experienced statin intolerance.

The American College of Cardiologists (ACC)/ American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) define myopathy as any muscle related disease, myalgia as muscle symptoms without CK elevation, myositis as muscle symptoms with CK elevation, and rhabdomyolysis as muscle symptoms associated with CK elevation >10 times the upper limit of normal (ULN) with serum creatinine elevation.<sup>5</sup>

In clinical practice any degree of muscle involvement is important as muscle symptoms could interfere with an individual's activities of daily living and quality of life. As statins are used for prognostic benefit and not for controlling any specific symptoms, drug therapy related adverse symptoms are likely to become a cause for poor compliance. Furthermore statin related muscle disease could interfere with the tolerability of exercise, depriving the individual of the cardiovascular benefits of regular exercising.

### **Clinical features and risk factors**

The symptoms of muscle disease include myalgia, tenderness, stiffness, cramping, weakness and fatigue. Among the PRIMO study participants who developed muscle problems, major sites of pain were the thighs, calves, or both, although about 25% of affected patients had generalized myalgia. In many, the pain or discomfort was intermittent and of variable duration. Twenty-five percent of affected patients reported tendon-associated pain. The temporal relation between statin therapy and the onset or resolution of myopathy is not fully defined. In the PRIMO study, patients developed muscle symptoms after a median of 1 month from initiation of statin therapy, ranging up to 12 months.<sup>3</sup>

Risk factors for statin-related muscle disease include high dose of a potent statin, history of

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myopathy while receiving another lipid-lowering agent, family history of statin-related myopathy, advanced age, female gender, hypothyroidism, alcoholism, renal failure, liver failure, recent major surgery, excessive physical activity and co-administration of drugs that inhibit statin metabolism.<sup>1</sup> Tolerability of high-intensity statin therapy is particularly low in those with an Asian ancestry.<sup>2</sup> Because simvastatin, lovastatin, and atorvastatin are primarily metabolized through the cytochrome P450 3A4 (CYP3A4) isoenzyme, inhibitors of CYP3A4 increase serum statin levels and their effects on susceptible tissues. Fluvastatin and rosuvastatin are less liable for drug interactions as their metabolism occurs via a different cytochrome enzyme system. Table 1 lists drugs that are known to increase the potential of myotoxicity when co-administered with statin therapy.

**Table 1. Drugs associated with statin interactions**

Amiodarone
Azole antifungals (itraconazole, ketoconazole, fluconazole)
Calcium Channel Blockers (verapamil, diltiazem)
Cyclosporine
Fibrates
HIV protease inhibitors
Macrolide antibiotics
Warfarin

## Management

Assessment of muscle symptoms in a patient receiving a statin should include evaluation of the risk factors for statin-related muscle disease as well as a search for other causes of muscle symptoms and CK elevation (Table 2).

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults<sup>6</sup> provides recommendations for management of statin-related muscle disease. The guideline recommends to avoid unnecessary discontinuation of statins, to obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy and to measure baseline CK level in individuals believed to be at increased risk for adverse muscle events. During statin therapy, routine measurement of CK level is not recommended but indicated in individuals with muscle symptoms. If unexplained severe muscle symptoms develop during statin therapy, prompt discontinuation and evaluation

**Table 2. Differential diagnosis of myopathy due to statin therapy**

Alcoholism
Cushing syndrome
Fibromyalgia
Hypothyroidism
Medications
Glucocorticoids
Antipsychotics
Antiretroviral drugs
Illicit drugs (cocaine or amphetamines)
Peripheral arterial disease (causes muscle cramps)
Polymyalgia rheumatica
Polymyositis
Systemic lupus erythematosus
Seizures
Tendon or joint disorders
Trauma
Unaccustomed physical exertion
Viral illness

for the possibility of rhabdomyolysis should be done. If the muscle symptoms are mild to moderate, discontinuation and further evaluation is still advised to determine other possible contributors (i.e. risk factors and other causes). If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy or if the predisposing condition has been corrected, treatment with the same statin could be resumed at the original dose. If a causal relationship exists between the original statin and muscle symptoms, a low dose of a different statin should be started once muscle symptoms resolve. The dose of the alternative statin could be gradually increased as tolerated, to achieve cholesterol targets. However these recommendations are made on limited evidence and the expert panel calls for further research in this area.

According to European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guideline on management of dyslipidaemia, CK level should be checked if a statin treated patient develops myalgia and the statin should be stopped if CK level is >5 times ULN.<sup>7</sup> No further recommendations are made with regard to reintroduction of statin therapy in this group. Furthermore no clear guidance has been

provided regarding the management of patients with intolerable muscle symptoms with CK < 5 times ULN.

There are no large randomized, controlled trials that can provide evidence as to how best to handle statin-related muscle problems. However several options have been described based on evidence from small studies. These options include switching of the statin, particularly to fluvastatin or low dose rosuvastatin, non-daily dosing regimens of statins, non-statin alternatives (eg. ezetimibe) and coenzyme Q10 supplementation.<sup>1,8</sup>

### Switching the statin

Although no trials have directly compared the incidence of statin-related muscle problems by agent, differences between different statins have been suggested. Head-to-head comparisons in the PRIMO study,<sup>3</sup> an observational study, showed that the proportion of patients with muscle-related symptoms was lowest with extended-release fluvastatin (5.1%) compared to pravastatin (10.9%), atorvastatin (14.9%), and simvastatin (18.2%). High statin dose and drug-drug interactions are risk factors for statin myopathy and the possible explanations for lower incidence of myopathy with fluvastatin are its high potency (therefore a lower dose can be used) and less liability for drug interactions as it is metabolized by a different system.<sup>1,9</sup>

Literature search failed to find any studies where fluvastatin therapy was directly compared with the other statins in patients with statin-related muscle problems. A randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of 12 weeks of treatment using extended-release fluvastatin 80 mg daily, alone; ezetimibe 10 mg daily alone; or the combination in 199 patients with symptomatic myopathy after receiving other statins.<sup>10</sup> Ezetimibe, extended-release fluvastatin and the combination lowered LDL cholesterol levels by 16%, 33%, and 46%, respectively. Proportions of patients achieving their target LDL cholesterol were: 29% with ezetimibe, 59% with extended-release fluvastatin, and 84% with the combination. Recurrent muscle symptoms occurred in 24% of patients receiving ezetimibe, 17% of patients receiving extended-release fluvastatin and 14% of patients receiving the combination therapy. There were no instances of creatine kinase increases  $\geq 10$  times upper limit of normal. Thus the authors concluded that in patients with previous statin intolerance extended-release fluvastatin alone or in combination with ezetimibe offers an effective and well-tolerated lipid-lowering option.

Between rosuvastatin and atorvastatin, rosuvastatin may be considered as a better option because it comparably decreases LDL cholesterol levels at approximately 50% of the dose of atorvastatin

and similar to fluvastatin, rosuvastatin metabolism occurs via a different cytochrome enzyme system in liver, making it less liable for drug interactions.<sup>1,9</sup> In a prospective, open-label pilot study,<sup>11</sup> 61 patients with previous statin intolerance due to myopathy (majority were on atorvastatin), received rosuvastatin 5 or 10 mg daily. Their mean reduction in LDL cholesterol level from baseline was 18% and 24%, respectively. Only one patient discontinued treatment because of myalgia, and none had elevation of CK. This pilot study suggested that low doses of rosuvastatin were safe and effective in patients with a history of statin intolerance. In a retrospective observational multicentre study, rosuvastatin 5mg was found to be tolerant and biochemically effective either as daily (n=134) or intermittent therapy (n=90) in 224 patients intolerant to other conventional statin regimens with simvastatin or atorvastatin.<sup>12</sup> The STELLAR Trial<sup>13</sup> which included 2,431 adults with hypercholesterolemia, reported that rosuvastatin had higher efficacy than pravastatin, atorvastatin and simvastatin, but the drug tolerability was similar across treatments. However the primary and secondary objectives of this trial were to assess efficacy and not safety. No evidence is available from clinical trials directly comparing rosuvastatin with atorvastatin in patients who have experienced statin-related myopathy.

### Non-daily dosing of statins

Atorvastatin and rosuvastatin have relatively long plasma half-lives of 15 and 20 hours, respectively,<sup>9</sup> and the duration of the cholesterol-lowering effect of statins is considerably longer than the duration of the pharmacokinetic half-life of these drugs. Therefore these two drugs are potentially suitable for non-daily dosing regimens to lower LDL cholesterol while possibly reducing the risk of adverse effects.

### Non-daily dosing of atorvastatin

A double-blind, placebo-controlled trial of 35 patients with hypercholesterolaemia which compared alternate-day atorvastatin versus daily atorvastatin over 12 weeks, showed that the alternate-day administration of atorvastatin can produce a reduction in LDL-C comparable to that of daily administration (LDL-C reduction: 35% and 38%, respectively).<sup>14</sup> The mean atorvastatin dose was higher in the alternate-day atorvastatin group (18 mg) than in the daily atorvastatin group (12 mg) at the end of the 12 weeks. However, no study has yet reported effects of alternate-day atorvastatin on muscle symptoms in patients with statin intolerance.

### Non-daily dosing of rosuvastatin

In contrast to atorvastatin, non-daily dosing of rosuvastatin has been evaluated in patients with

previous statin intolerance and these studies have shown more than 30% reduction in LDL cholesterol with no recurrence of muscle problems in the majority.<sup>1,15-17</sup>

A retrospective study reported 51 patients with previous statin intolerance who received rosuvastatin, 5 or 10 mg (mean, 5.6 mg/d), on alternate days for a mean duration of 4.6 months, where the mean LDL-C reduction was 34.5% enabling approximately 50% to achieve their LDL-C goal. The majority (72.5%) of patients had no recurrence of myalgia.<sup>15</sup> Joy et al reported a retrospective analysis of 14 patients who received non-daily dosing regimen of rosuvastatin and showed mean LDL-C reductions of 33.6% in 7 patients receiving a mean dose of rosuvastatin, 7.9 mg every other day; 27.5% in 6 patients receiving rosuvastatin, 5 or 10 mg 3 times weekly and 13.2% in 1 patient receiving rosuvastatin, 5 mg twice weekly.<sup>1</sup> There is a case report of two patients who were unable to tolerate daily atorvastatin therapy secondary to myalgia who tolerated rosuvastatin, 2.5 mg and 5 mg 3 times weekly, and had LDL cholesterol reductions of 20% and 38%, respectively.<sup>16</sup>

In a case series, once-weekly rosuvastatin, 5 to 20 mg, has resulted in statin tolerance and a mean LDL-C reduction of 29% among 8 patients with previous statin intolerance.<sup>17</sup> In an observational study of 50 patients with previous statin intolerance, once weekly rosuvastatin (doses ranging from 2.5 mg to 20 mg a week) was tolerated by 37 (74%) with significant changes in their lipid levels.<sup>18</sup> A randomized, double-blind, placebo-controlled crossover study involving 17 patients with statin intolerance due to myalgia which evaluated rosuvastatin 5 to 10 mg once weekly over a period of 8 weeks has shown that once-weekly low-dose rosuvastatin is an effective and well-tolerated lipid-lowering therapy option for patients who were previously unable to tolerate statins.<sup>19</sup>

Although these non-daily dosing regimens of rosuvastatin have not been proven to reduce cardiovascular events, they may be considered as a reasonable option for patients with statin intolerance who may otherwise be completely deprived of proven benefits of statin therapy until evidence from large randomized clinical trials become available.

### Ezetimibe

Ezetimibe has a mechanism of action which is different to that of the statins. It inhibits intestinal absorption of cholesterol. Therefore it is postulated that ezetimibe is less likely to cause muscle problems than the statins.

In a clinical trial involving 827 patients, ezetimibe monotherapy was associated with LDL-C reduction of about 18%.<sup>20</sup> In this clinical trial, the incidence of musculoskeletal pain was 3% and 4% among those who received ezetimibe and placebo respectively. The addition of ezetimibe to existing statin therapy causes LDL-C reductions similar to those achieved with higher doses of statin alone. In a double-blind study, 628 patients with primary hypercholesterolemia, LDL-C reductions with ezetimibe 10 mg plus atorvastatin 10 mg (50%) and 80 mg atorvastatin alone (51%) were similar. IMPROVE-IT,<sup>22</sup> a recently published large scale trial, showed a clear benefit of ezetimibe in reducing cardiovascular events when added to simvastatin in patients with acute-coronary-syndrome. However more insight is required regarding cardiovascular benefits of ezetimibe as monotherapy and in different patient groups.

There are no randomized controlled trials evaluating the effect of ezetimibe in patients with statin myopathy. In a retrospective, 3-month study evaluating the effect of ezetimibe alone in 25 patients with statin intolerance and ezetimibe plus low dose statin in 10 patients intolerant of high-dose statins, LDL cholesterol reductions were 26% and 20% respectively.<sup>23</sup> Ezetimibe was well tolerated by these patients and CK activity was not significantly affected. Based on the limited data available, ezetimibe alone or preferably in combination with low dose statin can be considered as an option in patients who are unable to tolerate statins due to muscle problems.

### Coenzyme Q10 supplementation

Coenzyme Q10 (CoQ10) supplementation is a popular therapy for statin myalgia despite limited and conflicting evidence of its efficacy. Statins block production of CoQ10 (ubiquinone), a component thought to be critical in mitochondrial function and cellular membrane integrity.<sup>24</sup> Therefore it is postulated that statin-induced CoQ10 deficiency causes mitochondrial dysfunction and interferes with normal aerobic metabolism in muscle, leading to skeletal muscle symptoms. Statin treatment reduces circulating levels of CoQ10. However the effect of statin therapy on intramuscular levels of CoQ10 is not clear and data on intramuscular CoQ10 levels in symptomatic patients with statin-associated myopathy are scarce.<sup>24-29</sup>

Supplementation can raise the circulating levels of CoQ10,<sup>9</sup> but data on the effect of CoQ10 supplementation on myopathy symptoms are scarce and contradictory. Results of a randomized trial involving 32 patients with statin myopathy who received either CoQ10 100 mg daily or vitamin E 400 IU daily, while

maintaining statin therapy, suggested that CoQ10 supplementation may decrease muscle pain associated with statin treatment.<sup>30</sup> Another trial involving 50 patients with statin myalgia, who were randomized to receive CoQ10 50 mg twice daily or placebo, showed that CoQ10 supplementation effectively reduced statin related mild-to-moderate muscular symptoms.<sup>31</sup> A pilot study evaluated the effect of CoQ10 supplementation on statin tolerance in 44 patients with previous statin-related myalgia. Patients were randomized to CoQ10 (200 mg daily) or placebo for 12 weeks in combination with upward dose titration of simvastatin from 10 mg daily, doubling every 4 weeks if tolerated to a maximum of 40 mg daily. This trial found no significant difference in myalgia score (assessed with a modified visual analogue scale), number of patients tolerating simvastatin therapy (40 mg daily) or number of patients who continued to receive therapy.<sup>32</sup> Another recently published 8-week, randomized, double-blind crossover trial evaluating CoQ10 600 mg daily versus placebo in 41 patients with simvastatin-induced myalgia failed to show a reduction in muscle pain with CoQ10 supplementation.<sup>33</sup> In a very recent meta-analysis of 6 studies with 302 patients, the conclusion was that available randomized controlled trials do not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy.<sup>34</sup>

Based on the available evidence, CoQ10 is not recommended for routine use in the management of statin myopathy. Larger, well-designed trials are required to evaluate this therapeutic option further.

## Conclusion

Muscle problems affect a significant number of patients receiving statin therapy. Statin-related muscle disease is likely to become an increasingly relevant problem because of recently defined stringent LDL cholesterol targets and the increasing number of patients prescribed statins. The paucity of outcome data and limited guideline recommendations for managing statin myopathy, has led many clinicians to adopt their individual clinical strategies, resulting in widely variable, non-evidence based practices. Currently, there is strong evidence for cardiovascular and mortality benefits of statins for individuals at risk. Therefore it is important that every effort is made to find a tolerable statin regimen for patients who have experienced statin-related muscle problems. The options include switching to rosuvastatin or fluvastatin, non-daily dosing regimens of statins and combination of ezetimibe with low dose statin therapy. Coenzyme Q10 supplementation is not recommended for routine use. Further research is warranted for the evaluation of strategies for managing statin induced myopathy and for the development of newer statins with lower potential for statin myopathy.

## Key Summary Points

Statin-related muscle disease can affect up to 10% of individuals taking statins but life threatening rhabdomyolysis is rare.

Individuals with muscle problems present with muscle pain, tenderness, stiffness, cramping, weakness or fatigue.

Risk factors for muscle disease include high dose of a potent statin, history of myopathy while receiving another lipid-lowering agent, family history of statin-related myopathy, advanced age, female gender, hypothyroidism, alcoholism, renal failure, liver failure, recent major surgery, excessive physical activity and co-administration of drugs that inhibit statin metabolism.

Assessment of statin-related muscle disease should include a search for other causes of myopathy.

Options for management of statin-related muscle disease include switching to rosuvastatin or fluvastatin, non-daily dosing regimens of statins and combination of ezetimibe with low dose statin therapy.

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