CASE STUDY

Statin-associated muscle adverse events
Some key issues explored

LEON A. SIMONS MD, FRACP

Muscle symptoms and signs often represent an important adverse event associated with statin therapy.

I have been asked to provide more detailed comment in the matter of statin-associated muscle adverse events (SAMAE). The National Lipid Association (NLA), a US-based educational organisation, has recently produced an updated assessment of statin muscle safety.[1] Although this assessment will not be the last word on the matter, it does provide an opportunity to revisit SAMAE.

Case scenario

Mr CE, a 53-year-old man, suffered an acute coronary syndrome in 2010. The culprit coronary lesion was identified and successfully stented, as were two lesions at other sites. In regard to coronary risk factors, he had no prior history of hypertension, had smoked 10 cigarettes per day over many years, and his father, a heavy cigarette smoker, had died from a heart attack at 59 years of age.

Mr CE's blood pressure in hospital was in the range of 140/86 to 130/80 mmHg. His body mass index (BMI) was 28.1 kg/m^2. His blood tests at initial presentation showed the following results:

- *total cholesterol 4.5 mmol/L (reference range <4.0 mmol/L)*
- *triglycerides 1.0 mmol/L (reference range <2.0 mmol/L)*
- *HDL-cholesterol 1.0 mmol/L (reference range >1.0 mmol/L)*
- *LDL-cholesterol 3.0 mmol/L (reference range <2.0 mmol/L).*

His levels of electrolytes, creatinine, glucose, liver enzymes and thyroid-stimulating hormone, as well as his blood count, all remained within normal limits. Dipstick urinalysis showed no abnormality.

Mr CE's progress in hospital was uncomplicated. He received standard dietary advice and assistance with smoking cessation, and was discharged on aspirin, clopidogrel, ramipril, metoprolol and atorvastatin 40 mg/day.

Consultant's comment

The above is a typical scenario for a first presentation of coronary artery disease. Many such patients have a combination of risk factors that are not necessarily of severe degree. Mr CE was middle-aged, a smoker, had a significant family history of coronary disease and had a modest excess of LDL-cholesterol. He was discharged on essentially standard therapy, except the dose of atorvastatin was half that used in relevant clinical trials. Some cardiologists are reluctant to prescribe atorvastatin at a dosage of 80 mg/day for fear of side effects, especially as Mr CE had only a modest excess of LDL-cholesterol.

Case scenario continued

Mr CE remained essentially well over the next two years, so clopidogrel was eventually suspended and other medications remained unchanged. His BMI was little changed, but he no longer smoked. His blood pressure averaged about 124/80 mmHg and his lipid profile was favourable with the following results:

- *total cholesterol 3.2 mmol/L*

Key points

- **Muscle symptoms and signs are the most frequent adverse events associated with statin therapy.**
- **These adverse events occur more frequently in routine care than in controlled clinical trials.**
- **Alternative causes must be excluded.**
- **Less frequent-than-daily dosing with another statin at a low dose may overcome muscle problems in some instances.**

CARDIOLOGY TODAY 2014; 4(4): 31-33

Professor Simons is Associate Professor of Medicine and Director at the University of NSW, Lipid Research Department, St Vincent's Hospital, Sydney, NSW.

Spectrum of statin-associated muscle adverse events

- Myalgia: unexplained muscle discomfort often described as 'flu-like' symptoms with normal CK levels. The spectrum of myalgia complaints includes:
  - muscle aches
  - muscle soreness
  - muscle stiffness
  - muscle tenderness
  - muscle cramps with or shortly after exercise (not nocturnal cramping)
- Myopathy: muscle weakness (not attributed to pain and not necessarily associated with elevated CK levels)
- Myositis: muscle inflammation
- Myonecrosis: muscle enzyme elevations or hyperCKaemia
  - mild >threefold greater than baseline untreated CK levels or normative upper limit that are adjusted for age, race and sex
  - moderate ⩾10-fold greater than untreated baseline CK levels or normative upper limit that are adjusted for age, race and sex
  - severe ⩾50-fold above baseline CK levels or normative upper limit that are adjusted for age, race and sex
- Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine level ⩾44 µmol/L – clinical rhabdomyolysis)

Abbreviation: CK = creatine kinase.
Reproduced with permission from Rosenson RS, et al. J Clin Lipidol 2014; 8(3 Suppl): S58-S71.[1]

- *triglycerides 1.2 mmol/L*
- *HDL-cholesterol 1.0 mmol/L*
- *LDL-cholesterol 1.7 mmol/L (reference range now <1.8 mmol/L).*

Standard safety tests remained favourable, in particular his creatine kinase (CK) level was satisfactory at 190 IU/L (reference range <200 IU/L).

For some months during the second year of follow up, Mr CE had noticed some degree of myalgia in his lower limbs after exercise, which he attributed to being unfit. However, these symptoms gradually became more persistent and more generalised and became associated with muscle weakness. Eventually, Mr CE consulted his GP who made a clinical diagnosis of statin-induced muscle problems. His CK level was not elevated (180 IU/L). There was a rapid resolution of all symptoms within a few days of cessation of atorvastatin.

After further discussion with his cardiologist and a washout period of four weeks, Mr CE was prescribed pravastatin 10 mg/day, which was later increased to 20 mg/day. Over the following year he remained free of any muscle symptoms, but with LDL-cholesterol level averaging 2.0 mmol/L. A compromise was declared in his overall management.

Consultant's comment

Although there is no definite proof that this patient manifested a SAMAE, the history is highly supportive of this diagnosis. The clinical story here is typical of one scenario – a patient fails to attribute muscle symptoms to statin therapy for a long period of time. A second scenario, not present in this case, relates to a patient who is misinformed by the pharmacist that a SAMAE will likely occur when starting statin therapy, or the patient obtains that same impression from consumer product information or other media and, sure enough, muscle symptoms eventually follow, possibly due to a placebo effect.

I will now focus on the salient points in the NLA report mentioned in my preamble,[1] but I will intersperse my personal observations as well.

The association of a statin with a muscle problem is generally a temporal relationship, yet causality is more difficult to prove. Although SAMAE may occur with any statin in solo therapy, when using simvastatin or atorvastatin in particular it may be related to a drug–drug interaction with inhibitors of CYP3A4 (e.g. macrolide antibiotics, antifungals, HIV protease inhibitors, gemfibrozil, cyclosporin, verapamil, diltiazem, amiodarone) or through other pathways. Other drugs may cause myopathic symptoms in their own right (e.g. substances of abuse, neuroleptics and psychotropic agents, immunosuppressants, antivirals, analgesic and anti-inflammatory drugs and fibrates). In addition, genetic, endocrine, infectious and immune disorders can present with muscle symptoms and signs.

SAMAE may present at any time after the beginning of statin therapy. The clinical findings may include muscle discomfort, ache, pain, stiffness, undue fatigue or cramps (myalgia), muscle weakness (myopathy), tenderness to palpation with or without muscle inflammation (myositis) and/or myonecrosis. The most severe form of myonecrosis is referred to as rhabdomyolysis. In this rare situation there is lysis of skeletal muscle cells, shifts in electrolytes and massive release of CK and myoglobin into the bloodstream. The latter may result in acute renal failure. The NLA has proposed a new working classification of SAMAE and this is presented in the box.[1]

Selected key issues addressed by the NLA 2014 update

Myalgia is the most common complaint in patients with SAMAE. It is more frequent in older patients and in those with either hypothyroidism or low vitamin D levels. It ranges in frequency from 1 to 5% in controlled clinical trials to 11 to 29% in observational studies.[1]

Because of a bias in patient selection, the incidence in clinical trials is likely to be a significant underestimate. On the other hand, the lack of standardised criteria in observational reports may lead to some overestimation of the true incidence. Two large retrospective studies in patients with supposed statin intolerance found that 92% and 73% of such patients could tolerate a different statin when rechallenged.[2,3]

Can statin-associated myalgia be reliably differentiated from myalgia due to a placebo effect?

The update said yes, but with limited scientific evidence. In a recent double blind trial, 202 participants naïve to statins were randomised to receive atorvastatin 80 mg/day or placebo for six months and they were evaluated regularly according to standardised questionnaires.[4] Of those on high-dose atorvastatin, 9.4% developed myalgia, and 4.6% did so on placebo. That is to say, 4.6% of patients on placebo had similar symptoms to those on atorvastatin.

Patients sometimes try cessation of the statin voluntarily, followed by a later rechallenge with the same therapy. The outcomes have been highly variable. Based on almost 30 years of observing patients taking statins, I cannot simply accept that the clinician can reliably differentiate placebo-induced myalgia from a statin-induced problem in every instance.

Are statin-associated muscle complaints altered by acute or chronic physical activity?

The update said yes, but again based on limited scientific evidence. In an observational study of almost 8000 outpatients in a usual care setting, the incidence of muscle pain with high-dose statin therapy increased with the level of physical activity, from 10.8% in those engaging in leisure-type activity to 14.7% in those regularly engaging in vigorous activity.[5] Other studies report an increase in CK levels after acute physical activity in people taking statins.

Anecdotally, I have observed many patients with elevated CK levels who were incidentally tested within a day or so of acute or unaccustomed physical activity. Blood testing should be avoided in this circumstance. Also anecdotally, some patients on statins have reported an increased tendency to tendon or muscle injuries after exercise.

Should a muscle biopsy be obtained in patients with SAMAE?

Although the update recommended muscle biopsy in very limited circumstances,[1] the report highlighted the need to exclude alternative causes of high CK levels (or muscle symptoms). These included physical activity issues, concurrent metabolic abnormalities (e.g. hypothyroidism, hypoparathyroidism, vitamin D deficiency, intermittent claudication), drug–drug interactions, acute alcohol toxicity or other myotoxic drug exposure, or intramuscular injection. If there is a family history of myalgia or longstanding myalgia prior to statin therapy, referral of the patient to a neurologist for further investigation is justified.

Can patients who are intolerant to one statin generally tolerate a different statin?

The update said yes, but again based on limited scientific evidence. Although there are some patients who are truly intolerant to the whole class of statin drugs, there are indeed patients who are intolerant to one statin drug and can often tolerate a different statin, as discussed above.[2,3] The report reviewed limited trial data suggesting that less-than-daily dosing of a different statin can sometimes be better tolerated. This might be once-weekly rosuvastatin at a low dose, with later dose or frequency adjustment as tolerated.[6,7] These dosing regimens have not been studied in terms of cardiovascular risk reduction.

I agree with this approach, but would extend this recommendation still further. I have observed many patients intolerant to atorvastatin who were able to tolerate rosuvastatin 2.5 to 5 mg once or twice per week and who achieved LDL-cholesterol lowering. However, another alternative here is low-dose pravastatin 10 to 20 mg/day, this being the most water-soluble statin available. Anecdotally, perhaps less than 25% of truly statin-intolerant patients will tolerate a different statin at a low dose.

Role of non-statin therapy – the use of supplements

The NLA update acknowledged that other drugs may have a place in statin-intolerant patients, namely ezetimibe or resins.

One symptom of vitamin D deficiency is myalgia, but there is little convincing evidence that vitamin D therapy will improve SAMAE. Anecdotally, supplemental intake of coenzyme Q10 has been claimed to reduce myalgia in patients with SAMAE. However, randomised controlled trials have failed to confirm this effect, but studies are ongoing.[1]

I have not found vitamin D or coenzyme Q10 to be helpful in this setting; nor can I report any real success at cholesterol control with popular alternative therapies such as lecithin, policosanol or low-dose niacin.

To quote the closing words in the NLA report: 'the patient who is highly resistive to any statin therapy, either because of previous actual or perceived side effects, or due to fear of developing side effects, presents a growing challenge to the clinician'.[1]

If such an option exists, the safest way to avoid return of SAMAE is to discontinue statin therapy. Sometimes, this comes down to quality of life issues. The potential benefit of statin therapy in a given patient might be heavily outweighed by the impairment in the quality of life. **CT**

References

1. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol 2014; 8(3 Suppl): S58-S71.
2. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med 2013; 158: 526-534.
3. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J 2013; 166: 597-603.
4. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. Circulation 2013; 127: 96-103.
5. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients – the PRIMO study. Cardiovasc Drugs Ther 2005; 19: 403-414.
6. Ruisinger JF, Backes JM, Gibson CA, Moriarty PM. Once-a-week rosuvastatin (2.5 to 20 mg) in patients with a previous statin intolerance. Am J Cardiol 2009; 103: 393-394.
7. Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. Am J Cardiol 2008; 101: 1747-1748.

COMPETING INTERESTS: None. The views expressed are purely those of the author.