Managing statin-induced myopathy

By Andrew Husband, MSc, MRPharmS

Statin have a substantial body of evidence supporting their use in the treatment of hypercholesterolaemia. However, the potential for muscle toxicity as a side effect from the use of statins is widely accepted. Post-marketing surveillance found that fatal rhabdomyolysis occurred in patients taking cerivastatin at a higher rate than that seen with other statins, prompting the drug’s withdrawal from the market in 2001.

Estimates suggest around 1.5 million people per year worldwide will experience myotoxicity related to statin use. Myopathy is a general umbrella term used to describe the spectrum of muscle problems that can present. Attempts to provide some uniformity for the diagnosis of muscle toxicity have led to the following definitions:

- Myopathy — general term for disease of muscle
- Myalgia — muscle symptoms without elevation of creatinine kinase (CK) levels
- Myositis — muscle symptoms with CK elevation <10 × upper limit of normal (ULN)
- Rhabdomyolysis — muscle symptoms, elevation of CK (≥10 × ULN) and potential myoglobinuria and renal failure
- Asymptomatic myopathy — elevated CK without muscle symptoms

Clinical presentation

Typically a patient will present with muscle pain, often described as cramps, or with diffuse discomfort in the legs. Focal pain is less suggestive of myopathy and more likely to be a strain or alternative diagnosis such as osteoarthritis. Increased nocturnal cramping is commonly reported. In other cases generalised weakness or fatigue, particularly following exercise, can occur. Such symptoms are reversible on stopping statin therapy and are unlikely to occur in patients who have been taking a statin for several years. Some small studies suggest that typical onset of muscle symptoms can range from one week to four years, with a mean duration before onset of 6.3 months.

The classification of myopathies for diagnostic purposes

Risk factors

Myotoxicity is dose-dependent and anything elevating the level of statin in the blood can increase the likelihood of muscle toxicity. Risk factors that predispose patients to developing myopathy with statin use include:

- Increasing age
- Female gender
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism

DISCUSSION POINTS

- How often do you consider the possible drug interactions that might influence the myotoxicity of a patient’s statin therapy? Knowledge of the individual CYP450 enzymes that metabolise different medicines will provide a more detailed understanding of interactions and their potential severity
- Should the pharmacist check whether the patient has experienced any muscle pain when issuing a repeat prescription? How can you articulate this without affecting the patient’s compliance?
- Are those patients on long-term therapies (such as statins) being given sufficient opportunity for therapeutic review to ensure their regimens remain suitable and appropriate? How can you and your colleagues contribute to this?
notable drug interaction that should be carefully considered before combination therapy is started.

Are all statins equal?
No direct head-to-head comparisons have been carried out assessing statin-induced myotoxicity. It has been suggested that lipophilic statins (such as lovastatin, simvastatin and atorvastatin) are more likely to cause myotoxicity because they cross the cell membrane of muscle cells more readily than the more hydrophilic ones (eg, pravastatin and rosuvastatin). There is insufficient evidence to support this theory fully and reports of rhabdomyolysis have been made in connection with both pravastatin and rosuvastatin — demonstrating that hydrophilicity is not the only factor determining myotoxicity.

Management
When a patient taking a statin reports muscle pain, a detailed history should be obtained. Other conditions that could be causing the problem, but are unrelated to statin therapy, should be ruled out — including osteoarthritis, tendinitis, radiolopathy and muscle strain.

Initial assessment should include measurement of CK. The magnitude of elevation will impact on how the patient is managed. Patients with CK elevations >10×ULN should be considered as potential rhabdomyolysis cases and investigated for elevated urine myoglobin levels and deteriorating renal function. Statin therapy should immediately be stopped.

For such patients the continued use of lipid-lowering therapy must be carefully balanced against the risks of further myotoxicity. Alternative non-statin therapy could be used or, should the perceived benefits outweigh the risks, reintroduction of a statin at a low dose with careful monitoring is possible.

For patients whose CK is elevated <10×ULN, statin therapy can be continued at the same or a lower dose providing muscle symptoms are tolerable. These patients should be monitored to ensure that CK levels are not continuing to rise and that symptoms remain the same. In the case of worsening symptoms, progressively rising CK levels or initially intolerable muscle symptoms, the statin should be stopped and the patient observed until symptoms resolve and the CK level returns to normal. For such patients, rechallenge with the same statin at a lower dose will often result in the patient continuing treatment without future myotoxicity.

**TEST YOURSELF**

1 Which of the following terms describes the most severe form of myotoxicity?
   a) Myopathy
   b) Rhabdomyolysis
   c) Polymyalgia rheumatica
   d) Myositis
   e) Asymptomatic myopathy

2 Which one of the following best describes the type of symptoms exhibited in statin-induced myopathy?
   a) Focal muscle pain
   b) Alopndy
   c) Diffuse, cramping pain
   d) Stabbing pain
   e) All of the above

3 Which of the following would not be considered to be a risk factor for statin-induced myopathy?
   a) Hypothyroidism
   b) >30% 10-year cardiovascular risk
   c) Renal dysfunction
   d) Concomitant medication
   e) Genetic polymorphism

4 Which of the following statins is considered to be hydrophilic?
   a) Simvastatin
   b) Cerivastatin
   c) Lovastatin
   d) Pravastatin
   e) Atorvastatin

5 Which of the following are associated with rhabdomyolysis?
   a) Altered hepatic function
   b) Nausea and vomiting
   c) Acute renal failure
   d) Visual disturbances
   e) None of the above

6 Which biochemical parameters should be checked routinely for a patient presenting with statin-induced myopathy?
   a) Creatinine kinase levels
   b) Erythrocyte sedimentation rate
   c) Thyroid function
   d) All of the above
   e) Answers a and c only

Other investigations should include thyroid function tests, since hypothyroidism can cause hypercholesterolaemia and elevated CK, and can predispose a patient to statin-induced myopathy. Muscle biopsy can be used to investigate statin-induced myopathy. Expert opinion suggests that this is unnecessary in most cases and a clinical approach to management, as outlined above, is more appropriate. Where patients do not recover despite cessation of statin therapy muscle biopsy might be indicated.

**Drug treatment**
It has been suggested that deficiency of coenzyme Q10 (ubiquinone) — another product of the pathway inhibited by statins — could cause mitochondrial dysfunction, leading to myopathy. Small-scale research has been undertaken to identify the role of coenzyme Q10 as a treatment for myopathy, with some positive results. Nonetheless, further study is required before this can be recommended as a routine treatment.

**Summary**
Statins are a widely prescribed and predominantly safe group of drugs for cholesterol lowering and reduction of cardiovascular morbidity and mortality. They are associated with a range of myotoxic side effects ranging from mild discomfort to life-threatening muscle damage and subsequent renal failure. Their safe use is dependent upon appropriate drug choice when initially prescribing and careful medicines management thereafter.

Pharmacists can help manage patients who take statins to ensure early identification of drug interactions or pharmacokinetic changes that might influence serum drug levels.

**References**

**Answers**
1; 2; 3; 4; 5; 6; 7; 8; 9; 10

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