

Statin Therapy: Is It Risky Business?

Although statin therapy is generally well tolerated, it should not be undertaken lightly, especially in the primary prevention of cardiovascular disease. What do you need to know about the adverse effects of statin treatment?

Alun Edwards, BA, MB, BChir, MRCP(UK), FRCPC

As presented at the University of Calgary's 28th Family Practice Review and Update (November 2003)

Statins have dramatically altered the approach to lipid lowering since their introduction in the late 1980s. A progressive increase in evidence from outcome-based, landmark clinical trials has provided sound justification for the widespread prescription of these agents.

The advances in efficacy and outcomes have been enhanced by the tolerability of statins. This is particularly true in comparison with the range of symptoms and discomfort caused by cholestyramine, colestipol and nicotinic acid, the principal lipid-lowering tools available previously.

Risk assessment is important. The decision to initiate therapy implies a long-term requirement to impact a risk factor that has failed to respond to lifestyle modification. Risk and cost effectiveness should be weighed.¹⁻³

How do I identify adverse effects?

Identifying adverse effects of drugs may not be straightforward. Rare

Mrs. Auden's Case

Mrs. Auden, 54, suffered a myocardial infarction two years ago. At that time, she was found to have Type 2 diabetes, and was treated with metformin. She currently takes acetylsalicylic acid daily, as well as an angiotensin-converting enzyme inhibitor. She also has mixed dyslipidemia (see box).

She was prescribed both simvastatin and atorvastatin, which had an excellent effect on her low-density lipoprotein cholesterol. However, simvastatin was discontinued because her alanine aminotransferase (ALT) was 84 U/l ($n < 50$), and atorvastatin was stopped due to

"muscle spasms". Her creatine kinase was 350 U/l when she had symptoms, but it has since persisted in the range of 300 U/l to 500 U/l, even though she denies any muscle pain or weakness. Her ALT also remains elevated at 70 U/l to 100 U/l, though it has been eight months since she last took a lipid-lowering agent.



Mrs. Auden's lipid profile

- LDL-C: 4.52 mmol/L
- HDL-C: 0.88 mmol/L
- TG: 3.37 mmol/L
- TC: 6.93 mmol/L

LDL-C: Low-density lipoprotein cholesterol
HDL-C: High-density lipoprotein cholesterol
TG: Triglycerides
TC: Total cholesterol

How should you manage Mrs. Auden?

effects may not become apparent until large numbers of patients have been exposed to the drugs. Confirmation of a drug-effect association also relies heavily on appropriate surveillance and dedication of clinicians in reporting events to government regulatory agencies—which is perhaps not the most dependable of activities. The situation is further compounded by the fact that patients most likely to benefit from statin therapy also suffer from other medical disorders. Patients with diabetes, for example, frequently require statin therapy to reach stringent low-density lipoprotein cholesterol (LDL-C) targets. However, these individuals are susceptible to a host of metabolic abnormalities and complications that might mask, or be misdiagnosed for, a drug-related adverse effect. Attention to the potential for adverse effects needs to continue.

New mechanisms of action in reducing atherosclerosis have emerged (pleiotropic effects) and there is even suggestion of benefit for diseases affecting other tissues (osteoporosis and Alzheimer disease). It would be unwise to rule out the potential of side-effects not yet contemplated.

Adverse effects with statins appear to fall into two main categories: hepatic- and muscle-related. Patients seem particularly troubled by hepatic disease, while physicians have been absorbed by the potential for myopathies.

About the author ...

Dr. Edwards is an associate professor, division of endocrinology and department of medicine, University of Calgary, and medical director, Calgary Health Region Diabetes Centre, Calgary, Alberta.

How is the liver affected?

Elevation in transaminase enzymes (most specifically alanine aminotransferase [ALT], and aspartate aminotransferase [AST]) is the functional hepatic abnormality associated with statin use. This abnormality of liver function tests is shared with other lipid-lowering drugs, fibrates, and nicotinic acid. It has also been suggested that, rather than reflecting hepatotoxicity, the enzymes “leak” from hepatocytes, whose cell membranes have been altered by lipid changes.⁴

It is increasingly recognized that patients with diabetes, or with the metabolic syndrome, are prone to a “fatty liver”; it is prudent to check ALT prior to commencement of statin therapy. We should, however, be reassured that pre-existing mild elevation of ALT in patients exposed to lovastatin is not predictive of progression to more serious increases of ALT (> 3 times the upper limit of normal).⁴ Most large clinical trials suggest that significant elevation of ALT occurs in < 2% of treated individuals.^{1,4,5} An analysis of all pravastatin trials revealed a rate of abnormal ALT at 1.4%, but this was equal to the rate in controls (untreated patients). Most cases of mildly increased ALT do not progress and, if they do, it is not associated with histologic evidence of damage.^{1,4-6}

The lack of a significant clinical hepatic problem is now leading to the suggestion that routine screening of ALT, which has been a longstanding safety recommendation, may not actually be necessary.⁷ Finding an abnormal ALT can either be handled by monitoring, switching to another statin, or rechallenging with the same statin after a drug holiday. Abnormal ALT levels should always prompt

Adverse effects with statins appear to fall into two main categories: hepatic-related and muscle-related.

consideration of other causes of hepatic dysfunction.

Rare severe acute hepatic necrosis has been suspected as a consequence of statin therapy, perhaps because preliminary animal studies revealed this problem with exposure to extremely high doses of statins. If this problem does occur, it is exceedingly rare in humans, occurring at no greater than one per 3 million patient-years exposure. The problem is idiosyncratic and of such rapid onset that periodic checking of ALT would not be of value.⁴

What is the impact on muscles?

Myopathies have long been recognized with statin use. Symptoms vary, but generally involve pain and tenderness in large muscle groups, occasionally with weakness. Terminology used in literature to describe these problems varies. Some terms include:

- myopathy, as a generic term,
- myalgia, which suggests muscle pain, and
- myositis, which implies pain with a concomitant elevation of creatine kinase (CK).⁶

Greater concern attends the risk of rhabdomyolysis with inflammatory disruption of muscle resulting in massively elevated CK levels, myoglobinuria, renal failure, and mortality.⁶

The precise frequency of muscle problems is not yet determined because of inconsistent definitions, and because of the frequency of abnormal CK levels (≤ 10 times the upper limit of normal) in completely asymptomatic individuals.^{5,7} Further confusing the diagnosis are reports of symptomatic individuals with biopsy-proven myositis, in whom CK levels were persistently normal.⁸ Therefore, although

Take-home message

- Adverse effects with statins are either hepatic- or muscle-related.
- Elevation in transaminase enzymes (ALT and AST) is the hepatic abnormality associated with statins.
- Cerivastatin was removed from the market because of its association to about three rhabdomyolysis-related deaths per million prescriptions.
- Abnormalities of ALT may not progress and rarely indicate risk of severe hepatic disease; routine monitoring of ALT may not be necessary.
- Routine monitoring of CK is not indicated, but should be measured in patients with muscle symptoms.
- Though adverse effects are low, patient education and clinician wariness are important in statin therapy.

CK is the most convenient laboratory tool for clinicians to assess drug-related myopathy, it is unreliable. Clinical judgment is required in dealing with a symptomatic patient.

There appears to be no excess risk of myopathy for various statins in comparison with controls in large clinical trials, with rates around 0.2%.^{1,9} Real-life, retrospective reviews of patients in general practice suggest muscle symptoms are more common in statin-treated patients, though fibrates were much more likely causes of myopathic complaints.¹⁰

Rhabdomyolysis is rare. Fatality rates for currently available statins range from 5% to 10%, or 0.04 to 0.2 per million prescriptions.^{9,11} Cerivastatin was removed from the market because of its association to about three rhabdomyolysis-related deaths per million prescriptions. Those prone

to this complication are the very elderly, patients with diabetes or chronic renal failure, or individuals on complex, multiple drug regimens.⁹

Routine monitoring of CK is unwarranted.⁵⁻⁷ Patients should be counselled about the potential for muscle symptoms. If symptoms present, then CK should be measured, although a normal value doesn't exclude statin-related myositis. It is probably safe to initiate statin therapy in patients with asymptomatic elevation of CK, while considering other causes of this result (*e.g.*, physical activity and hypothyroidism).


What about drug combinations with statins?

Combination of statins with certain agents appears to increase the risk of myopathies. The drugs implicated are inhibitors of cytochrome P450 (CYP3A4). These inhibitors increase circulating levels of lovastatin, simvastatin, and atorvastatin, with the potential to increase the risks of rhabdomyolysis tenfold. Cyclosporin, erythromycin, azole antifungals, and diltiazem are the major culprits behind myopathies. There is a concern that high-volume consumption of grapefruit juice can also cause problems.⁹

The other significant interaction is with fibrates, particularly gemfibrozil. Gemfibrozil was implicated in 12 of the 31 cases of fatal rhabdomyolysis, leading to cerivastatin's withdrawal as a therapeutic agent.¹¹

In limited studies of combination fibrate/statin therapy, only 1% of patients had asymptomatic CK elevation, and a further 1% had to discontinue therapy due to myalgias.^{1,9} This is a therapeutically valuable combination which is used to treat mixed dyslipidemias. Patient education, to emphasize early presentation with muscle-related symptoms, is important.

So, should I be wary of statin therapy?

Statins deserve their reputation as highly effective agents in the prevention of CVD, and they have a very low risk of adverse effects. Patients and physicians can be reassured with the data from trials and clinical experience, though vigilance for known and novel adverse effects is warranted. A recent community-based survey suggests the prevalence of idiopathic polyneuropathy is increased in statin users; though this is a rare condition, it provides warning of the need for continued wariness.¹² 

References

1. Gotto AM: Safety and statin therapy: Reconsidering the risks and benefits. *Arch Intern Med* 2003; 163(6):657-9.
2. Clark LT: Treating dyslipidemia with statins: The risk benefit profile. *Am Heart J* 2003; 145(3):387-96.
3. Abookire SA, Karson AS, Fiskio J, et al: Use and monitoring of statin lipid-lowering drugs compared with guidelines. *Arch Intern Med* 2001; 161(1):53-8.
4. Tolman KG: The liver and lovastatin. *Am J Cardiol* 2002; 89(12):1374-80.
5. Dujovne CA: Side-effects of statins: Hepatitis versus "transaminitis" — myositis versus "CPKitis". *Am J Cardiol* 2002; 89(12):1411-3.
6. Pasternak RC, Smith SC, Bairey-Merz CN, et al: ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation* 2002; 106(8):1024-8.
7. Smith CC, Bernstein LI, Davis RB, et al: Screening for statin-related toxicity: The yield of transaminase and creatine kinase measurements in a primary care setting. *Arch Intern Med* 2003; 163(6):688-92.
8. Phillips PS, Haas RH, Bannykh S, et al: Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002; 137(7):581-5.
9. Thompson PD, Clarkson P, Karas RH: Statin-associated myopathy. *JAMA* 2003; 289(13):1681-90.
10. Gaist D, Rodríguez LA, Huerta C, et al: Lipid-lowering drugs and risk of myopathy: A population-based follow-up study. *Epidemiology* 2001; 12(5):565-9.
11. Staffa JA, Chang J, Green L: Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; 346(7):539-40.
12. Gaist D, Jeppesen U, Andersen M, et al: Statins and the risk of polyneuropathy: A case control study. *Neurology* 2002; 58(9):1393-7.