

## Statin-induced Myopathy

Myopathy is an uncommon but potentially fatal adverse reaction to statins, which is usually preventable. The aim of this bulletin is to highlight this risk.

### Some facts

Statins are associated with three muscle syndromes: myalgia (muscle complaints without serum creatine kinase (CK) elevation); myositis (muscle symptoms with CK elevation); and rhabdomyolysis (markedly elevated CK concentration, usually >10 times the upper limit of normal, with an elevated serum creatinine consistent with myoglobin-induced nephropathy).<sup>1</sup> Rhabdomyolysis may result in hyperphosphataemia, due to release of phosphate from the damaged myocyte, and resultant hypocalcaemia. Rhabdomyolysis is fatal in 10% of cases, due to renal failure or cardiac arrest from hyperkalaemia. The incidence of rhabdomyolysis with simvastatin is approximately 0.03% at 20mg, 0.08% at 40mg, and 0.5% at 80mg daily in clinical trials.<sup>2</sup> The actual risk is likely to be higher, as patients in trials are often younger with fewer co-morbidities and taking fewer interacting drugs than the population who actually take simvastatin or atorvastatin.

CARM has 15 reports of patients developing rhabdomyolysis with statins (13 of these were for simvastatin); two patients died.<sup>3</sup> Most of the cases presented with muscle pain or weakness, or with dark urine, following a recent dose increase, or the addition of an interacting drug.

The risk of myopathy from statins is dose-related. Simvastatin and atorvastatin are both metabolised by CYP3A4 (and to a lesser extent, CYP2C8), so CYP3A4 inhibitors will increase their plasma concentrations. Pravastatin, the only other statin available in New Zealand, is not metabolised by the CYP pathway and thus does not share the CYP interactions.<sup>4</sup>

### Risk factors for statin-induced myopathy:<sup>5</sup>

- Age >70 (women at higher risk than men)
- Frailty and small body frame
- Concurrent disease (eg. renal failure, heart failure, diabetes, hypothyroidism)
- Solid organ transplant recipients
- Patients in the perioperative period
- Patients on high doses
- Patients on interacting drugs

### Monitoring for myopathy

All patients should be asked about muscle pain or weakness, especially during the first 3 months of therapy, after a dose increase, or after addition of an interacting drug. The statin should be stopped if CK is found to be >10x upper limit of normal (ULN), and urine checked for myoglobin. If CK is 3-10x ULN, CK should be checked

weekly and the patient assessed for interactions, and consideration of dose reduction or stopping the drug.

### Precautions/contraindications

- In patients with a CrCL of <30ml/min, the recommended maximum dose of simvastatin is 10mg/day. If CrCl <10ml/min, the recommended maximum dose is 5mg/day, with close monitoring.<sup>6</sup>
- Avoid if AST or ALT >3x ULN at outset. Caution in patients with previous liver disease or alcohol abuse.
- Statins are contraindicated in pregnancy or lactation.

### Important statin interactions

Interacting drug	Mechanism	Action	Risk
Macrolides <sup>A</sup>	3A4 inhibition	avoid combination	high
Azole antifungals <sup>B</sup>	3A4 inhibition	avoid combination	high
Gemfibrozil	pharmacodynamic & 2C8 inhibition	max simv dose 10mg	high
Other fibrates	pharmacodynamic	max simv dose 10mg	high
Protease inhibitors	3A4 inhibition	avoid simv. Max atorv dose 10mg	high
Danazol	3A4 inhibition	max simv dose 10mg	mod
Ciclosporin	3A4 inhibition	max simv dose 10mg	mod
Nicotinic Acid (>1g/day)	Pharmacodynamic	max simv dose 10mg	mod
Amiodarone	3A4 inhibition	max simv dose 20mg	mod
Verapamil & diltiazem	3A4 inhibition	max simv dose 20mg	mod
Fusidic acid	3A4 inhibition	avoid combination	high
Grapefruit juice	3A4 inhibition	avoid if on statin	mod-high

A) Macrolides includes erythromycin & clarithromycin (roxithromycin & azithromycin are weak CYP3A4 inhibitors)

B) Azoles includes itraconazole, fluconazole & ketoconazole

### References:

- 1) Thompson PD et al. Statin-associated Myopathy. JAMA 2003, 289(13): 1681-90
- 2) Prescriber update (Medsafe) 2004;25(1), May
- 3) Personal correspondence, Dr R Savage, NZ Pharmacovigilance Centre, University of Otago.
- 4) Neuvonen PJ et al. Drug interactions with lipid-lowering drugs: Mechanisms and clinical relevance. Clin Pharm & Ther;80(6): 565-575, 2006
- 5) Vasudevan AR, Hamirani YS, Jones PH. Safety of statins: Effects on muscle and the liver. Cleveland Clinic Journal of Medicine 2005 72(11): 990-1002
- 6) Lipex datatsheet, Medsafe