Statins: myalgia and myositis

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The topic of side effects of statin therapy has become more prominent since the precautionary withdrawal of cerivastatin following reports of death and rhabdomyolysis with this particular statin, especially when given in simultaneous combination therapy with gemfibrozil. In addition, many patients complain of myalgia with statins; this side effect has an incidence of up to 5%. There is a tendency for earlier use of statins in coronary care units because of improved compliance and the possibility of a reduction in peri-infarction events in registry studies, although the MIRACL trial of atorvastatin in acute coronary syndromes did not show any significant differences in hard end points at 16 weeks.[1]

Statins have a rapid onset of action with effects being seen on lipids within one to two weeks.[2] The open label, prospective study of 12 patients by Samarasinghe *et al.* in this issue (pages 209-14) confirmed these effects on lipid profiles but also monitored creatine kinase (CK) profiles to assess the potential confounding effect of concomitant statin therapy on markers of myocardial infarction.[3] No difference in CK levels was observed except in one patient who had a drug-dependent rise in CK from 100 IU/L to 250 IU/L with simultaneous myalgia.

Myositis

The slight rise in CK would be consistent with mild myositis, which is associated with painful muscles and CK elevation. Withdrawal of statin therapy is indicated in patients whose CK rises 10-fold to levels of about 2,000 IU/L. These levels occur in about 0.1% of patients in randomised, controlled trials. Lesser elevations of CK are rarely recorded, although data from a cohort of 200 patients with familial hypercholesterolaemia,[4] whose creatine kinase elevations at baseline and in response to exercise exceed those with polygenic hypercholesterolaemia, showed no significant change in CK at three months with either simvastatin or atorvastatin therapy.[5]

The extreme form of myositis is rhabdomyolysis with plasma CK > 20,000 IU/L, myoglobinuria and extreme muscular pain. This idiosyncratic side effect occurs in one in 250,000 patients and is commoner in females, the elderly, hypothyroidism and with concomitant therapy with cytochrome P_{450} 3A4 metabolised drugs, including cyclosporin, erythromycin and fibrates (especially gemfibrozil).[6] The mechanism of rhabdomyolysis is obscure but changes in cellular 'high-energy' phosphate metabolism, through effects on creatine phosphate or the ubiquinone-related mitochondrial synthesis of adenosine triphosphate (ATP) metabolism, are potential candidates.[7] Case reports exist of creatine supplement-induced rhabdomyolysis in athletes implicating muscle phosphate metabolism in this syndrome.[8]

Myalgia

Myalgia is far commoner and not accompanied by any CK elevation. The mechanism is also obscure but it has been noticed that by inhibiting hydroxy-methyl-glutaryl (HMG)-CoA reductase, statins also reduce isoprenoid intermediates of cholesterol synthesis, including those that are utilised in the manufacture of ubiquinone which is essential for electron transport in the mitochondria.[9] Carnitine supplements are often used to treat metabolic myopathies by increasing fatty acyl-CoA entry to mitochondria and may reduce risks of rhabdomyolysis in some patients with disorders of fatty acid or carnitine metabolism.[10] Some anecdotal reports also suggest that supplementation with ubiquinone (co-enzyme Q_{10}) at doses of 30 mg reduces symptoms of myalgia in a proportion of patients with metabolic myopathies.[11] Statins should deplete ubiquinone levels through their action on reducing cholesterol synthesis,[9,12,13] but this effect is not seen on plasma levels in all studies[14] possibly due to differences in methods of measurement.[15] If intracellular ubiquinone depletion does occur, then basic science studies suggest doses of ubiquinone up to 200 mg may be needed to completely normalise electron transport and plasma levels.[16] Unfortunately, no randomised, placebo controlled trials have been performed of this simple nutritional remedy for a common side effect of statins.

With the increasing use of higher doses of statins and widening of the therapeutic indications for these drugs, as trial evidence favours lower low density lipoprotein (LDL) cholesterol targets, the incidence of patients unable to tolerate these agents is likely to increase. Unfortunately, few studies have investigated how to manage these side effects apart from reducing the dose or avoiding statin therapy. The use of cholesterol-uptake inhibitors – such as ezetimibe to reduce LDL cholesterol through alternative mechanisms, or possibly novel compounds inhibiting squalene synthase, which are theoretically capable of raising isoprenoid levels and hence possibly restoring ubiquinone levels – may offer alternative methods of attaining LDL targets without requiring high doses of statins. However, if part of the action of statins is through dose-dependent effects on isoprenoid metabolism, rather than increasing LDL-receptor expression, then these novel agents may prove less effective than statin monotherapy. Thus, potential exists for the use of agents that directly address the muscle side effects of statin therapy without compromising their efficacy. Formal investigations of the potential role of co-enzyme Q_{10} and other supplements in the management of statin-induced myalgia need to be performed.

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