

COMMENTARY

Statins: is there a need for alternative or adjunctive therapy?

In the few years since their introduction into clinical practice the 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase inhibitors, or statins, have captured the market for cholesterol lowering drugs. They display virtually all the attributes of the ideal hypolipidaemic agent. Total plasma cholesterol falls by 15–30% and low density lipoprotein (LDL) cholesterol by 20–40% while high density lipoprotein (HDL) cholesterol rises by 5–10% in response to regular treatment.¹ As a bonus there is a welcome though less spectacular reduction of 10–20% in plasma triglyceride. Considerable aggregate clinical benefits accrue from these changes. The recently published results of the Scandinavian Simvastatin Survival Study (4S) indicate that simvastatin treatment of individuals with pre-existing evidence of coronary heart disease reduced their subsequent coronary mortality by 42%, their need for coronary revascularisation procedures by 37%, and, most importantly, their overall death rate by 34%.²

The statins work by suppressing endogenous cholesterol synthesis in the liver.³ This triggers an increase in the number of LDL receptors on hepatocyte membranes and as a result promotes the hepatic uptake of LDL to compensate for the deficit. Plasma concentrations of LDL cholesterol therefore fall. Are the statins now the unassailable ultimate choice for cholesterol reduction and coronary heart disease prevention? Clearly not. Of the 2221 subjects in the 4S Study who were randomised to statin treatment, only 71% achieved their targeted cholesterol reduction after one year of treatment.² No doubt in many, if not most, cases this was owing to poor compliance. However, as clinical experience with these drugs grows it is becoming apparent that they have variable effects on blood lipids. Resistance to their actions is greatest in patients with heterozygous familial hypercholesterolaemia, who do not respond adequately in terms of LDL cholesterol reduction and require a coprescription of a second cholesterol lowering agent. Moreover, the statins are less discriminating in their ability either to target specific atherogenic LDL subspecies or to raise the circulating mass of putatively antiatherogenic HDL; and they are certainly not the best treatment for hypertriglyceridaemia. Consequently, it is not surprising that there has been growing enthusiasm to tailor therapy to the specific lipid abnormality by combining statins with various other hypolipidaemic agents.

Fibric acid derivatives are the second most commonly prescribed class of lipid lowering drugs. They exert their principal actions by promoting the lipolysis of triglyceride-rich lipoproteins and limiting the availability of free fatty acids for triglyceride synthesis in the liver.⁴ Plasma triglyceride concentrations therefore fall precipitously (by 50% or more) during treatment, and this is accompanied by important qualitative reductions in the atherogenicity of LDL and increases in the cardioprotection offered by HDL. The complementarity of these effects with the cholesterol lowering actions of the statins argues for the combined use of these drugs in the treatment of patients with increases in both cholesterol and

triglyceride, the most common lipid abnormality seen in individuals with existing coronary heart disease. Analysis of a score of such published studies in 516 patients over the past five years shows that consistent clinically useful gains in the reduction of total cholesterol, triglyceride, and LDL cholesterol and an increase in HDL (compared with either agent used separately) when statins and fibrates are used in combination.⁵ Most of these studies featured gemfibrozil combined with lovastatin: but simvastatin has also been used with gemfibrozil, bezafibrate, and fenofibrate; and pravastatin has been used with gemfibrozil and bezafibrate. But do the lipid lowering benefits of the combination offset the potential risks of treatment? Each drug class on its own has been shown to be both acceptable to patients and very safe. None the less, both have been linked individually to myopathy; and in combination⁶ they may increase the risk of this adverse event.

A review of the myopathic incidents that were recorded in the 20 studies discussed above shows that serum creatine kinase, used as a surrogate for muscle damage, was rarely increased.⁵ Any rise was usually symptom free and transient and did not require withdrawal of therapy. Muscle pain leading to drug withdrawal developed in less than 1% of treated individuals; and in no case was there evidence of life-threatening rhabdomyolysis or myoglobinuria. A report by Feher and his colleagues on pages 14–17 substantiates this earlier finding.⁷ In their retrospective analysis of 102 patients who received a statin-fibrate combination for more than one year, four individuals developed a creatine kinase concentration that exceeded the upper reference value. None developed myalgic symptoms. Of course, it is not unlikely that such a rare side effect (1% or less) will be inappropriately represented in Feher's small sample, or even in the 500 patients aggregated from the 20 recent studies.⁵ We therefore need to develop a different perspective on the magnitude and severity of the problem by examining post-marketing surveillance and drug reaction data. This approach of course suffers from the weakness of being unable to define the numbers of patients who require to be given combined drug therapy in order to generate one case of myopathy.

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