Editorial

High dose simvastatin and adverse muscle effects

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High blood cholesterol, or hyperlipidemia, is a cardiovascular risk factor. Surveys have demonstrated that 35.6% of adults in the United States suffer from hyperlipidemia.[1] Currently there are various therapeutic regimens available for hyperlipidemia. The use of lipid-lowering drugs, patient education, dietary modification, and exercise have all been recommended for the management of hyperlipidemia.[2]

Among the lipid-lowering drugs, the most effective and best-tolerated agents are the statins, which decrease LDL-cholesterol production in hepatoctyes by competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Because of their LDL cholesterol–lowering potency, the statins are the most effective in reducing cardiovascular risks, with the highest decrease in serum LDL-cholesterol being due to rosuvastatin 40 mg (63%), atorvastatin 80 mg (57%), and simvastatin 80 mg (46%).[3] However, statin therapy also has a high incidence of adverse effects, particularly affecting skeletal muscle and the liver, with the statin-induced myopathies being the most recognized. Statin myopathies range from asymptomatic increases in creatine kinase concentration to muscle aches or weakness to fatal rhabdomyolysis (in ascending order of severity). The risk of statin-induced myopathy increases with the lipophilicity, cholesterol-lowering potency, and dosage of the drugs. With the exception of cervastatin, all lipophilic statins (simvastatin, fluvastatin, lovastatin, atorvastatin) are metabolized by cytochrome P450 3A4 (CYP3A4) enzymes via first-pass metabolism in the gastrointestinal tract and liver. Inhibition of first-pass metabolism by competing substances using the same pathway may increase statin toxicity from 5% to 100%.[4] Damage to skeletal muscle is commonly assessed by determining the concentration of creatine kinase (CK), an enzyme essential for maintaining ATP stores in skeletal muscle.[4] Most definitions of myopathy involve a higher than tenfold rise in serum creatine kinase concentration.[5]

In the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH),[6] involving approximately 12,000 subjects with past myocardial infarction and randomly assigned in approximately equal numbers to receive 80 mg and 20 mg simvastatin, myopathy was defined as a serum creatine kinase level exceeding 10 times the upper limit of normal, accompanied by unexplained muscle weakness or pain. The most severe form of statin myopathy is rhabdomyolysis, with muscle cell destruction or enzyme leakage. Rhabdomyolysis is defined as unexplained muscle pain or weakness with a serum creatine kinase level of more than 40 times the upper limit of normal.[7]

The SEARCH trial found 98 (1.6%) cases of definite or incipient myopathy among the 6,000 subjects on 80 mg simvastatin, during approximately 6 years of follow-up, but only 2 definite and 6 incipient cases of myopathy in the 20 mg group (0.1%). Although the SEARCH

and other clinical trials have generally found a relatively percentage of statin-induced myopathy (<5%), In clinical practice, myalgias occur in 5–10% of patients receiving statins.[6]

The statin myopathies are presumably the result of inhibition of mevalonate synthesis, causing depletion of its metabolites, such as cholesterol, isoprenoids, and coenzyme Q19. Lack of these substances causes abnormal membrane behaviors, impaired intracellular signaling, and decreased mitochondrial respiratory function, respectively. In a genomewide association study, as part of the SEARCH trial, genetic predisposition to statin myopathy was demonstrated to be associated with a variant of the *SLCO1B1* gene that is common among individuals of European ancestry.[6] The *SLCO1B1* gene encodes an organic anion transporter that regulates the hepatic uptake of statins and other drugs. Single nucleotide polymorphism (SNP) analysis of *SLCO1B1* found a strong association of myopathy with the rs4363657 and rs4363656 SNPs within the *SLCO1B1* gene. The rs4363656 C allele has a prevalence of 15% in the population. The cumulative risk for myopathy in individuals taking 80 mg daily of simvastatin was 18.0% for CC homozygotes, 3.0% for the CT genotype, and 0.6% for the TT genotype.

Collective evidence indicates that individuals with the C allele of the rs4149056 *SLCO1B1* genotype have higher statin blood concentrations, suggesting that this allele is a high-risk allele for statin-induced myopathy. The percentage of simvastatin-induced myopathy attributable to variant *SLCO1B1* is approximately 60%. Therefore, the incidence of simvastatin myopathy could be reduced by 60% if simvastatin were not prescribed to individuals homozygous or heterozygous for the variant allele. On the other hand, prescribing low-dose simvastatin to heterozygous individuals only, and none to homozygous individuals, would result in a 25% reduction in myopathy incidence. This approach merits to be more fully evaluated.[8]

Based on the SEARCH trial and other data on the risks of high-dose (80 mg) simvastatin, the US Food and Drug Administration (FDA) has recently instituted safety-labeling changes and related measures to prevent the prescription of high-dose simvastatin to new patients. If during the year 2012 these measures prove to be ineffective, high-dose simvastatin may ultimately be withdrawn from the market.[9] Currently, high-dose simvastatin should be prescribed only to patients who have been using the drug for at least one year without clinically significant muscle toxicity. In addition, because simvastatin is extensively metabolized by the CYP3A4 enzyme system, the drug should not be used concomitantly with other drugs metabolized by CYP3A4, such as antifungal azoles, macrolide antibiotics, HIV protease inhibitors, and nefazone. Moreover, simvastatin at a dosage of more than 10 mg should not be used concomitantly with gemfibrozil, cyclosporine, and danazol. Amiodarone and verapamil should not be used concomitantly with a simvastatin dose of more than 20 mg, while diltiazem should not be used concomitantly with a simvastatin dose of more than 40 mg.

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