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EDITORIAL COMMENT

The Pharmacogenetics of Statin Therapy

When the Body Aches, the Mind Will Follow*

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Despite the increasing prevalence of cardiovascular risk factors such as obesity, diabetes, and hyperlipidemia in the U.S., there has been a surprising decrease in cardiovascular mortality among patients with various presentations of coronary artery disease (1). It is likely, if not certain, that a large reason for this decline is the increased use of HMG-CoA reductase inhibitors to lower serum cholesterol and promote stabilization of atherosclerotic plaque. Despite high levels of statin adherence in clinical trials, other studies have suggested poor adherence in high-risk patient populations, particularly the elderly (2,3). Although the safety data for this class of medications suggest a very low incidence of severe adverse reactions, such as rhabdomyolysis and myopathy, myalgias without serum creatine kinase (CK) elevation remain a common side effect and the most common reason for discontinuation of therapy. Although myalgia appears to be a class effect (it has been described with all available agents), there is a significant amount of variability within the class, which has lead to the investigation of genetic determinants of statin metabolism and toxicity.

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The safety of statin therapy has been vigorously debated during the last decade, and the balance of clinical trial data has been reassuring. Cerivistatin was removed from the market after multiple cases of severe myopathy and rhabdomyolysis, and this led to focused scrutiny of all other available agents. Randomized trials involving tens of thousands of patients have been performed demonstrating the safety and efficacy of simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, and lovastatin. Although each agent has a unique pharmacology and drug interaction profile, when used as monotherapy for hyperlipidemia, there is a very low incidence of severe toxicity. In a meta-analysis of 65,000 patients treated with statin or placebo, there was no increased risk of rhabdomyolysis among patients treated with statins (4). An analysis of 11 managed care plans revealed only 24 cases of hospitalization for rhabdomyolysis over 252,000 patient-years (5). However, the use of high doses of statins in combination with other drugs that alter their metabolism can lead to increasing blood levels with consequent risk of liver or muscle toxicity. This has been demonstrated for virtually all available agents, but most commonly for agents metabolized by the CYP450 3A4 enzyme. Simvastatin in particular has been associated with an increased risk of rhabdomyolysis when taken in combination with multiple inhibitors of CYP3A4 (6).

In this issue of the *Journal*, Voora et al. (7) report the results of the STRENGTH (Statin Response Examined by Genetic Haplotype Markers) study, and suggest that reduced-function single nucleotide polymorphisms (SNPs) of the *SLCO1B1* gene may be responsible for myopathy and myalgia. *SLCO1B1* encodes the enzyme OATP1B1, responsible for liver transportation of statins. This study was unique because in addition to confirming the previously suggested association between reduced function alleles for this gene and CK elevation, they also confirmed an association between the *SLCO1B1*5* allele and myalgia symptoms without CK elevation. Elevated levels of simvastatin metabolites (but not pravastatin) were seen among patients with the targeted SNP. These exciting results demonstrate for the first time that there may be a strong genetic susceptibility to both myopathy and statin-induced myalgias in the absence of elevated serum CK, and that genetic testing may provide important prognostic information to guide individualized statin therapy.

The *SLCO1B1* gene has previously been identified as a likely factor in the development of simvastatin-induced myopathy (8). In a genomewide study of approximately 300,000 markers among 85 subjects with confirmed myopathy from in the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) study, the odds ratio for myopathy was 16.9 for patients with homozygous reduced-function SNPs at this locus. The role of *SLCO1B1* in the metabolism of other statins remains unclear. The STRENGTH study suggests that pravastatin metabolites are not significantly elevated in patients with the homozygous *SLCO1B1* genotype. There was an increase in the risk of myalgia among SNP carriers taking atorvastatin; however, the difference was not statistically significant. No other agents were studied, and it is unknown whether the same findings could be replicated for rosuvastatin, lovasatin, and fluvastatin.

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Despite these exciting findings and their clinical relevance, they likely do not tell the whole story. Each individual statin agent is dependent upon liver uptake for its biologic effect; however, the dependence on transporter proteins such as OATP1B1 vary according to agent. Lipophilic statins can enter the liver via passive diffusion, whereas hydrophilic statins require active transportation. Fluvastatin, for instance, has previously been shown to have pharmacokinetic properties that are independent of genetic variation at the *SLCO1B1* locus (9). *SLCO1B1* polymorphism has previously been shown to increase blood levels of simvastatin acid (10). The search is on for additional genetic variants that may alter statin metabolism and cause adverse events.

The analysis by Voora et al. (7) also confirms a previous association between female sex and adverse events among patients receiving statin therapy. Although the exact mechanism of this interaction is unknown, it is likely multifactorial. It is possible that female sex attenuates the activation of metabolizing enzymes. It is also likely that lower mean body weight and muscle mass affects the volume of distribution of some statin agents, making females more susceptible to elevated circulating drug levels. These findings suggest that lower doses of simvastatin should be considered in female patients, and that changing agents is a reasonable alternative in both males and females with likely statin-induced myalgias even in the absence of elevated serum CK.

Further studies will undoubtedly identify other genetic factors associated with adverse reactions to statin agents. For now, the risk of severe reactions is fortunately rare and not likely to be improved by routine genetic testing. One of the important issues that require additional investigation is the role of *SLCO1B1* in patients taking statin agents other than simvastatin. The OATP1B1 enzyme is responsible for the transport of multiple statins, but it remains unclear whether the genetic variants will have a similar effect on the incidence of myalgias and myopathy. Voora et al. (7) found a nonsignificant increase in myopathy among carriers of the *SLCO1B1* alleles among patients taking atorvastatin, but found no increase in myopathy among patients taking pravastatin. Previous research indicates that the enzyme encoded by *SLCO1B1* affects simvastatin and pravastatin metabolism, but not fluvastatin (9,10). The data by Voora et al. (7) suggest that simvastatin acid may be a more clinically important substrate for this transporter enzyme.

Genetic testing may someday become an important adjunct to risk stratification among patients with cardiovascular disease. The prediction of adverse events based on genetic variation is a focus of intense investigation for statins, ADP receptor antagonists, and warfarin. It seems reasonable, for now, to choose a statin based on known drug interactions, particularly CYP450 interactions, and goal low-density lipoprotein level. High doses should be reserved for patients at intermediate to high risk of recurrent vascular events, and particular care should be taken to screen for muscle symptoms among patients requiring high-dose therapy. If a patient develops myalgias or CK elevation while taking simvastatin, a SNP at the *SLCO1B1* locus should be suspected, and changing agents may provide relief of symptoms. Further studies should examine the role of the OATP1B1 enzyme in the transport and metabolism of rosuvastatin and atorvastatin, 2 of the most commonly prescribed agents currently available. The elimination of myalgias has the potential to dramatically improve statin adherence and, therefore, clinical outcomes, and the vigilance of investigators in the field supports our current level of optimism that genetic testing will one day become an important clinical tool.

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