Polymorphisms in transporter genes can have profound effects on statin pharmacokinetics. In particular, a common genetic variant of organic anion–transporting polypeptide 1B1 reduces the hepatic uptake of many statins, increasing the risk of statin-induced myopathy. Similarly, genetically impaired adenosine triphosphate (ATP)-binding cassette G2 transporter efflux activity results in a marked increase in systemic exposure to various statins. Importantly, the effects of these genetic polymorphisms differ depending on the specific statin that is used. This provides a rational basis for the individualization of lipid-lowering therapy.

Statins are among the most widely used drugs worldwide. They are usually very well tolerated, but they can cause myopathy as a rare, plasma concentration–dependent adverse reaction.1 Symptoms of statin-induced myopathy include fatigue, muscle pain, muscle tenderness, muscle weakness, and cramping, which can occur with or without an increase in the blood concentration of creatine kinase. The clinical spectrum of statin-induced myopathy ranges from a mild and relatively common myalgia to a life-threatening and rare rhabdomyolysis.

Statins differ considerably in their pharmacokinetic characteristics.3,10–15 Simvastatin and lovastatin are administered in an inactive lactone form and are converted to an active acid form in the body, whereas other statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, pitavastatin) are administered in the active acid form. The main clearance mechanism for the more lipophilic statins is oxidative biotransformation, whereas the more hydrophilic statins (pravastatin, rosuvastatin) are excreted mainly in the unchanged form. Simvastatin, lovastatin, and atorvastatin are metabolized primarily through CYP3A4, and fluvastatin is metabolized mainly through CYP2C9.1 Although these characteristics are important determinants of many drug–drug interactions affecting statin pharmacokinetics, all statins are also substrates of membrane transporters, which have been shown to play an important role in statin disposition. Importantly, certain transporters display significant genetic polymorphism, which affects the pharmacokinetics and toxicity of statins.

Transporter Pharmacogenetics and Statin Toxicity

M Niemi1

SLCO1B1 AND STATINS

SLCO1B1 encodes the organic anion–transporting polypeptide 1B1 (OATP1B1) influx transporter, which is expressed on the basolateral membrane of human hepatocytes.2 Consequently, OATP1B1 mediates the hepatic uptake of its substrates from portal blood. In addition to OATP1B1, two other OATP transporters—OATP1B3 and OATP2B1—are expressed on the hepatocyte basolateral membrane in quantities roughly similar to that of OATP1B1.3 Two common single-nucleotide polymorphism (SNP) variants of the SLCO1B1 gene—c.388A>G (p.Asn130Asp; rs2306283) and c.521T>C (p.Val174Ala; rs4149056)—have been shown to affect the transport function of OATP1B1.4 The effects, however, depend on their combination in individual haplotypes. When the c.388A>G exists without the c.521T>C SNP, the haplotype is termed SLCO1B1*1B; it is usually associated with increased activity of OATP1B1 and therefore with lower plasma concentrations of OATP1B1 substrates.5,6 The c.521T>C SNP reduces the transport activity of OATP1B1 and increases the plasma concentrations of OATP1B1 substrates, both in the SLCO1B1*5 (c.521T>C alone) haplotype and in the SLCO1B1*15 (c.521T>C along with c.388A>G) haplotype.7,8 The low-activity SLCO1B1*5 and *15 haplotypes (i.e., c.521C allele) have a combined allele frequency of ~15–20% in Caucasians, 10–15% in Asians, and 2% in sub-Saharan Africans and African Americans.9 The SLCO1B1*1B haplotype has a frequency of ~25–30% in Caucasians, 40% in South/Central Asians, 60% in East Asians, and 80% in sub-Saharan Africans and African Americans.9

All statins are substrates of OATP1B1,3,10–15 but the effects of SLCO1B1 polymorphism differ depending on the specific statin that is used. The effect is largest on simvastatin; the area under the plasma concentration–time curve (AUC) of active simvastatin acid has been shown to be 221% greater in individuals with the c.521CC genotype than in those with the c.521TT genotype (Figure 1).13 The AUC of atorvastatin was shown to be 162–191% greater (weighted mean 181%),15–17 that of pravastatin was 144% greater,18 that of pitavastatin was 57–130% greater (weighted mean 90%),7,8,15,19,20 and that of rosuvastatin was 62–117% greater (weighted mean 87%)18,21,22 in individuals

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1Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland. Correspondence: M Niemi (mikko.niemi@helsinki.fi)

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with the c.521CC genotype than in those with the c.521TT genotype. Individuals with the c.521TC genotype generally display modestly increased AUC values that lie between the values for individuals with the c.521TT and those for individuals with the c.521CC genotype. The SLCO1B1 c.521T>C SNP has no effect on the pharmacokinetics of fluvastatin. The differences in the effects of SLCO1B1 polymorphism on the pharmacokinetics of individual statins may be partly explained by varying contributions of other OATPs to their hepatic uptake. For example, fluvastatin and rosuvastatin are also substrates of OATP1B3 and OATP2B1,12,23,24 pravastatin and atorvastatin are substrates of OATP2B1,3,10,14 and pitavastatin is a substrate of OATP1B3.12

The SLCO1B1*1B/*1B genotype has been associated with a 35% reduction in the AUC of pravastatin relative to the SLCO1B1*1A/*1A genotype but does not seem to affect the pharmacokinetics of rosuvastatin. The effects of the SLCO1B1*1B/*1B genotype on the pharmacokinetics of other statins are unknown. Although most pharmacokinetic studies have been single-dose studies, one study that involved multiple doses found that the effects of SLCO1B1 polymorphism on pravastatin pharmacokinetics are similar after a single dose and after a 3-week treatment.25

The SLCO1B1 c.521T>C SNP is strongly associated with simvastatin-induced myopathy (Figure 2). Approximately 300,000 genome markers were determined in 85 patients who had developed myopathy while receiving 80 mg simvastatin daily and in 90 controls without myopathy. A noncoding SNP in the SLCO1B1 gene, which is in nearly complete linkage disequilibrium with the c.521T>C SNP, was associated with myopathy at a genome-wide significance level. More than 60% of the myopathy cases could be attributed to the c.521T>C SNP, with an odds ratio of 4.5 per copy of the c.521C allele. The association was seen to be replicated in a study of 20,000 patients receiving 40 mg simvastatin daily, yielding a relative risk of 2.6 per copy of the c.521C allele. Moreover, the c.521T>C SNP was associated with a slight reduction in the cholesterol-lowering efficacy of simvastatin, whereas the c.388A>G SNP was associated with a slightly enhanced efficacy. These findings are consistent with the hypothesis that the c.521T>C SNP is associated with a reduction in hepatic uptake and that the *1B haplotype is associated with an enhancement in uptake. It is probable that the SLCO1B1 c.521T>C SNP is associated with an increased risk of myopathy in the case of most other statins as well; however, the risk attributable to the c.521T>C SNP probably depends on the specific statin that is used.

ABC2 AND STATINS

ABC2 encodes the ATP-binding cassette G2 (ABC2) efflux transporter, also known as breast cancer resistance protein. ABC2 is expressed in the apical membranes of intestinal
epithelial cells, hepatocytes, and renal tubule cells and in the endothelial cells that form the blood–brain barrier. Therefore, ABCG2 may limit intestinal absorption and tissue penetration and enhance the renal and hepatic elimination of its substrates. One relatively common SNP, c.421C>A (p.Gln141Lys; rs2231142), reduces the transport function of ABCG2. The ABCG2 c.421C>A SNP has a frequency of ~10–15% in Africans and African Americans, 27,28

Most statins are substrates of ABCG2. The AUC of rosuvastatin was 144% greater, that of inactive simvastatin lactone 111% greater, and those of atorvastatin and fluvastatin 72% greater in individuals with the ABCG2 c.421AA genotype than in those with the c.421CC genotype (Figure 1).28,29 These increases in plasma concentration are most likely due to increased bioavailability of the orally administered drug, as a consequence of decreased intestinal efflux of these statins by ABCG2 in association with the c.421AA genotype. The ABCG2 genotype has no significant effect on the pharmacokinetics of pravastatin and pitavastatin. It is probable that these findings translate into an increased risk of muscle toxicity in individuals with the c.421AA genotype who use rosuvastatin, atorvastatin, and fluvastatin, whereas the consequences for simvastatin therapy are more difficult to predict. However, no studies have yet been published on the clinical effects of ABCG2 polymorphism in the context of statin therapy.

**OTHER TRANSPORTERS AND STATINS**

In addition to OATP1B1 and ABCG2, many statins are also substrates of other transporters that display significant genetic variability, such as the multidrug resistance protein 1 and multidrug resistance–associated protein 2 (MRP2) efflux transporters that are expressed in the apical membranes of intestinal epithelial cells, hepatocytes, and renal tubule cells. The ABCB1 (encoding multidrug resistance protein 1) haplotypes c.1236C-c.2677G-c.3435C and c.1236T-c.2677T-c.3435T have relatively minor effects on the pharmacokinetics of atorvastatin and simvastatin acid (55–60% greater AUC in TTT/TTT individuals as compared with CGC/CGC individuals) (Figure 1).31 These ABCB1 haplotypes have no significant effect on the pharmacokinetics of fluvastatin, lovastatin, pravastatin, and rosuvastatin. However, given that the CGC and TTT haplotypes are relatively common (allele frequencies: 34 and 43%, respectively, in Caucasians), 31 they may play some role in the variability of statin pharmacokinetics at the population level. A rare synonymous SNP (c.1446C>G; frequency ~1–2.5% in Caucasians) in the ABC2C gene, encoding MRP2, has been associated with pravastatin pharmacokinetics. 33 The AUC of pravastatin was 67% lower in individuals who are heterozygous for this SNP than in noncarriers, probably as a consequence of increased expression of MRP2. Other ABC2C SNPs that were shown to be associated with MRP2 expression in some studies (e.g., c.-24C>T, c.3563T>A, and c.4544G>A) have not been shown to be associated with pravastatin pharmacokinetics. 20,33 There appear to be no studies on the effects of ABC2C polymorphism on the pharmacokinetics of other statins.

Pitavastatin and rosuvastatin are substrates of OATP1A2, a influx transporter that is expressed (among other sites) in intestinal epithelial cells. However, it is not known whether genetic variability in SLCO1A2 affects statin pharmacokinetics. Moreover, certain SNPs in the genes encoding the OATP2B1 (SLCO2B1), organic anion transporter 3 (SLC22A8), and bile salt export pump (ABCB11) transporters have not shown any association with pravastatin pharmacokinetics. 7,8,20

**CLINICAL IMPLICATIONS**

Because the SLCO1B1 c.521T>C SNP markedly reduces the hepatic uptake, increases the plasma concentrations of active simvastatin acid, and enhances the risk of myopathy during high-dose simvastatin therapy (Figure 2), it is obvious that high-dose simvastatin therapy should be avoided in carriers of this SNP. Given that statin-induced myopathy is a concentration-dependent adverse reaction, it is advisable to also avoid high doses—particularly of atorvastatin and pitavastatin and probably also of rosuvastatin and pravastatin—in carriers of this SNP. On the basis of the currently available pharmacokinetic and toxicity data, maximum doses can be recommended for each genotype (Figure 3). It should be noted that, because the effects of SLCO1B1 polymorphism differ between individual statins, treatment alternatives exist for each genotype. Genotyping for a single SNP can be achieved rapidly and at a low cost. SLCO1B1 genotyping should therefore be used to increase the safety of high-dose statin therapy in clinical practice.

Analogously, ABC2G2 genotyping could also be used to guide statin therapy in clinical practice. Because ABC2G2 and OATP1B1 are not parallel systems, it is likely that their effects on statin pharmacokinetics are additive. However, as there are currently no data related to ABC2G2 polymorphism–induced clinical effects in the context of statin therapy, one may argue that further studies are needed before any recommendation can be made for routine genotyping of patients for the polymorphism prior to initiating statins. This argument could be applicable to ABCB1 genotyping as well. However, it is foreseeable that, in the future, individualization of statin therapy will be best achieved.
via combined genotyping for various transporter (and other) genes that affect the pharmacokinetics and pharmacodynamics of statins.

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CONFLICT OF INTEREST
The author declared no conflict of interest.