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Expert Review

Influence of Drug Transporter Polymorphisms on Pravastatin Pharmacokinetics in Humans

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Abstract. The role of drug transporters in pravastatin disposition is underlined by the fact that pravastatin does not undergo significant cytochrome P-450 (CYP)-mediated biotransformation. The organic anion transporting polypeptide 1B1 (OATP1B1), encoded by *SLCO1B1*, and multidrug resistance-associated protein 2 [MRP2 (*ABCC2*)], are thought to be the major transporters involved in the pharmacokinetics of pravastatin in humans. Other transporters that may play a role include OATP2B1, organic anion transporter 3 (OAT3), bile salt export pump (BSEP), and the breast cancer resistance protein (BCRP). OATP1B1 and MRP2 mediate the hepatic uptake and biliary excretion of pravastatin, respectively. The *SLCO1B1* and *ABCC2* polymorphisms probably contribute to the high interindividual variability in pravastatin disposition. Recent small studies have characterized the impact of the *SLCO1B1* polymorphism on pravastatin in humans, and especially the c.521T>C single-nucleotide polymorphism (SNP) seems to be an important determinant of pravastatin pharmacokinetics. Pravastatin plasma concentrations may be up to 100% higher in subjects carrying the c.521C variant, as found in the **5*, **15*, **16*, and **17* haplotypes, reflecting diminished OATP1B1-mediated uptake into the major site of pravastatin elimination, the liver. The *SLCO1B1* polymorphism seems to have a similar impact on the pharmacokinetics of single- and multiple-dose pravastatin. Overall, 2–5% of individuals in various populations may be expected to show markedly elevated plasma pravastatin concentrations due to the *SLCO1B1* polymorphism. Of note, the impact of the *SLCO1B1* polymorphism on statins may be dependent on ethnicity. Although individuals with a diminished hepatic uptake of pravastatin might be expected to show reduced cholesterol-lowering efficacy due to lower intracellular pravastatin concentrations, there is preliminary evidence to suggest that the *SLCO1B1* polymorphism is not a major determinant of non-response to pravastatin. The possible consequences of drug transporter polymorphisms, especially the *SLCO1B1* and *ABCC2* polymorphisms, for the lipid-lowering efficacy and tolerability of pravastatin in various ethnic groups warrant further study.

KEY WORDS: drug disposition; OATP; pravastatin; transporter; vectorial transport.

PHARMACOKINETICS OF PRAVASTATIN

The oral bioavailability of pravastatin, a semisynthetic inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is relatively low, about 18%, due to poor intestinal absorption and high hepatic first-pass extraction (1,2). The low lipophilicity of pravastatin (3) and extrusion of absorbed drug back into the gut lumen by efflux transporters probably contribute to the poor absorption of pravastatin. Further, pravastatin is unstable in acidic conditions (4,5), and interindividual differences in gastric acidity may contribute to the variable bioavailability of pravastatin.

As a hydrophilic compound, pravastatin is not significantly metabolized by the cytochrome P-450 (CYP) enzymes (6). Although CYP3A4 and some other CYP enzymes may contribute to the formation of hydroxylated metabolites from pravastatin (7–9), these pathways account for only a small fraction of the total elimination of pravastatin (4). Accordingly, potent inhibitors of CYP3A4, CYP2C9, or CYP2C19 had no significant effects on the pharmacokinetics of pravastatin in healthy volunteers (10,11). Pravastatin is excreted to a large extent unchanged in bile and urine, and biliary excretion is the major route of elimination (2). Although CYP-mediated biotransformation is of little significance to pravastatin disposition, a high interindividual variability is evident in the pharmacokinetics of pravastatin. For example, in a study with ten healthy Caucasian volun-

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ABBREVIATIONS: AUC, area under the plasma concentration–time curve; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; C_{max}, peak concentration in plasma; CYP, cytochrome P-450; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; MRP, multidrug resistance-associated protein; NTCP, sodium-dependent taurocholate cotransporting polypeptide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; SNP, single-nucleotide polymorphism.

teers, the area under the plasma concentration–time curve (AUC) of pravastatin varied about 12-fold (10).

ROLE OF DRUG TRANSPORTERS IN THE DISPOSITION OF PRAVASTATIN

Pravastatin is a substrate of several drug transporters, including the organic anion transporting polypeptide 1B1 (OATP1B1, previously known as OATP-C/OATP2/LST-1), encoded by *SLCO1B1* (12–14) and the efflux transporter multidrug resistance-associated protein 2 [MRP2 (*ABCC2*)] (15) (Fig. 1). Pravastatin and several other statins are actively transported from the portal blood into hepatocytes by the uptake transporter OATP1B1 (14,16–21), which is located on the basolateral (sinusoidal) membrane of hepatocytes (20,22–24). MRP2 is expressed in the apical (canalicular) membrane of hepatocytes, in the apical membrane of the proximal tubule of the kidney, and in the apical membrane of enterocytes in the duodenum and jejunum (23,25,26). MRP2 may thus reduce the gastrointestinal absorption and facilitate the biliary and renal excretion of its substrate drugs.

Transporters that may play a limited role in the disposition of pravastatin include the uptake transporters OATP2B1 [previously known as OATP-B (*SLCO2B1*)] (27) and organic anion transporter 3 [OAT3 (*SLC22A8*)] (28) and the efflux transporters bile salt export pump [BSEP (*ABCB11*)] (29) and breast cancer resistance protein [BCRP (*ABCG2*)] (30). In addition to the liver, OATP2B1 is expressed in the small intestinal enterocytes (27), where it may facilitate the absorption of pravastatin. OAT3 may contribute to the urinary excretion of pravastatin in humans (28). BSEP and BCRP are expressed in the canalicular membrane of hepatocytes (31,32) and may contribute to the biliary elimination of pravastatin, especially in the absence of MRP2. BCRP is also expressed in the small intestine (32), where it may reduce pravastatin absorption. The balance of evidence from several *in vitro* studies suggests that pravastatin is not a substrate of P-glycoprotein (*ABCB1*, *MDR1*) (33–36).

In vivo studies investigating drugs inhibiting drug transporters have given useful information about the role of various transporters in pravastatin disposition, although the lack of specific inhibitors limits the ability to probe the influence of individual transporters on overall drug disposition. Concomitant treatment with cyclosporine, a potent OATP1B1 inhibitor (37), has been associated with a several-fold increase in plasma concentrations of pravastatin and several other statins (6,19,38–40), suggesting that OATP1B1 plays an important role in the disposition of many statins. It should, however, be noted that cyclosporine may inhibit also other drug transporters, including P-glycoprotein (41) and MRP2 (42). On the other hand, the P-glycoprotein inhibitor itraconazole did not show statistically significant effects on plasma pravastatin concentrations among ten healthy volunteers (10), which is in agreement with the results from the *in vitro* studies characterizing pravastatin as a P-glycoprotein substrate (33–36).

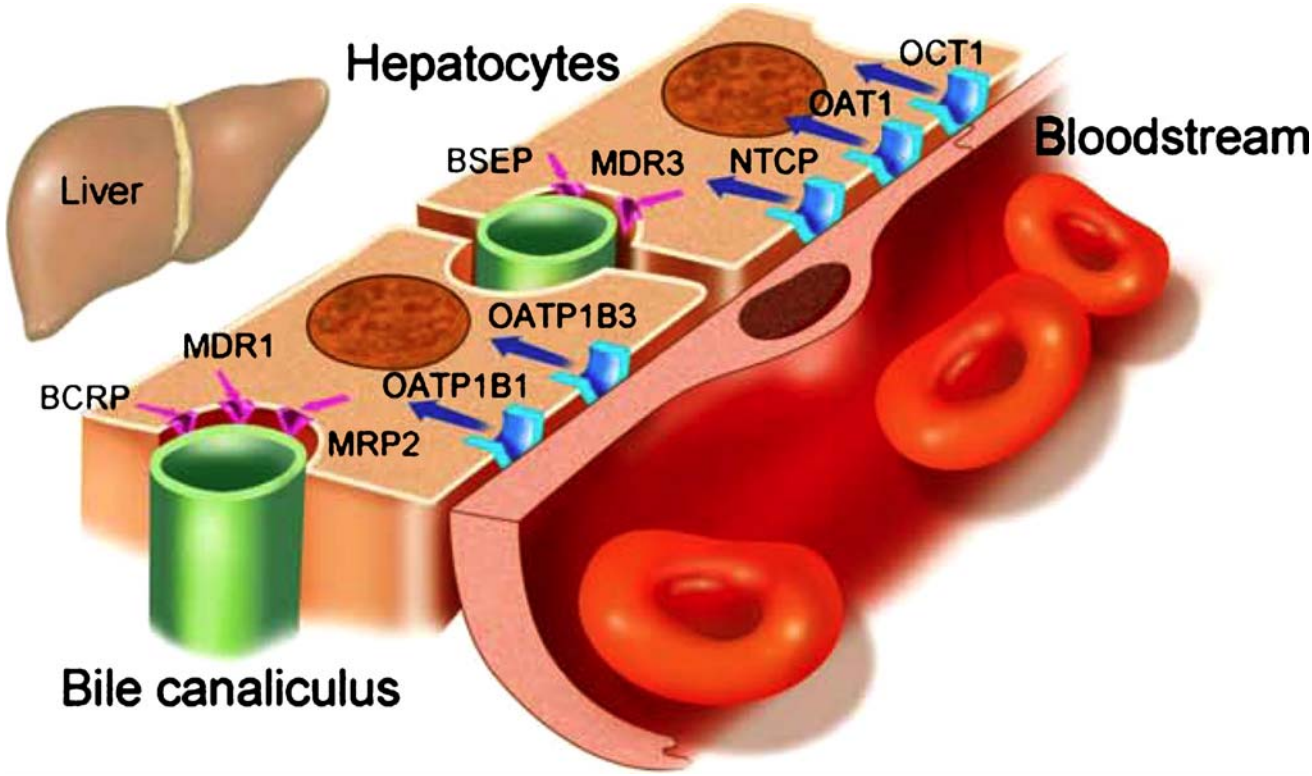

Fig. 1. In the liver, the coordinated expression and activity of uptake (e.g., OATP1B1) and efflux (e.g., MRP2) transporters mediates vectorial transport of exogenous (drugs) and endogenous substrates from the portal bloodstream into the bile. Drugs may undergo further biotransformation in the hepatocyte or be excreted unmodified into bile, as in the case of pravastatin (reprinted from (20) with permission from the American Society for Clinical Pharmacology and Therapeutics).

INFLUENCE OF DRUG TRANSPORTER POLYMORPHISMS ON PRAVASTATIN PHARMACOKINETICS

OATP1B1

Considering the localization of OATP1B1, it is reasonable to assume that impaired function of OATP1B1 would result in reduced hepatic uptake of pravastatin and thus in increased systemic exposure to pravastatin. In fact, expression and function of OATP1B1 is considered the rate-limiting step in the hepatic clearance of pravastatin and other statins (43,44). Thus, diminished OATP1B1-mediated uptake of pravastatin limits its entry into the major site of elimination (hepatocyte) (2), which is reflected in accumulation of pravastatin in plasma (Fig. 2). Effects of the *SLCO1B1* polymorphism on the transport activity of OATP1B1 *in vitro* and on the pharmacokinetics of pravastatin in humans have been investigated in a number of recent studies. Single-dose studies have shown that plasma concentrations of pravastatin after a dose of 10–40 mg are considerably higher in Caucasian and Japanese healthy volunteers with certain *SLCO1B1* single-nucleotide polymorphisms (SNP), especially c.521T>C ($Val^{174}Ala$) (45–48). In Caucasians, this SNP exists in four major haplotypes which can be distinguished by the promoter SNPs g.−11187G>A and g.−10499A>C and the c.388A>G non-synonymous SNP (47,49). These haplotypes are g.−11187G/g.−10499A/c.388A/c.521C (**5*), GAGC (**15*), GCGC (**16*), and AAGC (**17*) (49). Of these haplotypes, at least **5*, **15*, and **17* have been associated with increased plasma concentrations of pravastatin (46–48).

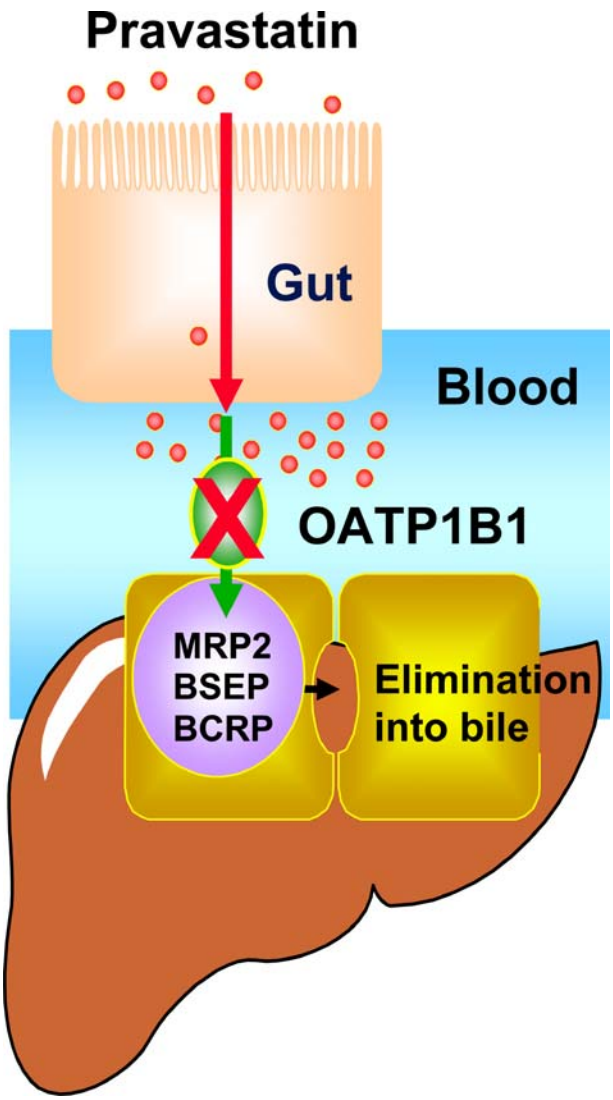

Fig. 2. A scheme that depicts the pharmacokinetic consequences of reduced OATP1B1 activity for pravastatin. Uptake of pravastatin into the site of elimination, the liver, is diminished and the drug accumulates in blood.

It may be noted that the *SLCO1B1* c.521T>C SNP was associated with elevated plasma concentrations of also rosuvastatin and pitavastatin in recent single-dose studies (50,51). The c.521CC genotype was associated with increased rosuvastatin concentrations in Caucasian subjects (there were no individuals homozygous for the variant c.521C allele among the Chinese, Malay, or Asian-Indian subjects studied) (51). However, there was no difference in the exposure to rosuvastatin between the c.521TT (wild-type) and c.521TC genotypes in any of the ethnic groups, including the Caucasians. Of note, it has been recently demonstrated that several transporters are capable of mediating the hepatic uptake of rosuvastatin (44). At least in the case of rosuvastatin, involvement of other hepatic uptake transporters might lessen the *in vivo* functional impact of reduced OATP1B1-activity. The study on the effects of *SLCO1B1* polymorphism on pitavastatin was carried out in Korean subjects only (50).

The c.521T>C SNP has been consistently linked with reduced transport activity of OATP1B1 both *in vitro* (14,52–54) and *in vivo* (45–47,55), but results regarding the *in vitro* functional effects of another common variant, the c.388A>G ($Asn^{130}Asp$) SNP, have been conflicting (14,52–54,56–58), with most studies indicating lack of effect on transport activity of several OATP1B1 substrates, including pravastatin. In a recent *in vitro* study, the transport activity of OATP1B1 for pravastatin was reduced by the c.521T>C SNP irrespective of whether the SNP was in the same haplotype with the c.388A>G SNP or not (14). Further, the c.388A>G SNP alone did not alter the *in vitro* transporting activity of OATP1B1 for typical substrates in HeLa or HEK293 cells, in contrast to the haplotypes **5* and **15* (14).

There are no published studies concerning the functional significance of the SNPs found in the promoter region of *SLCO1B1* (i.e., g.−11187G>A, g.−11110T>C, and g.−10499A>C) (47). However, the g.−11187G>A SNP was associated with increased plasma concentrations of pravastatin in humans, pravastatin concentrations being especially high in subjects heterozygous for the **17* haplotype (47). This finding might be explained either by an effect of the g.−11187G>A SNP on *SLCO1B1* transcription or by its relatively strong linkage with the c.521T>C SNP (49).

Three small studies have shown that plasma pravastatin concentrations are significantly higher in subjects with certain *SLCO1B1* SNPs or haplotypes (45–47). In the study of Nishizato *et al.* (45), carried out in Japanese subjects, significant differences between heterozygous carriers of the

15 haplotype and subjects with the reference genotype were found in the oral clearance of pravastatin, but not in the AUC. In any event, the results of these studies are fairly consistent, suggesting a 50–100% increase in plasma pravastatin concentrations in Caucasian and Japanese carriers of the *5*, *15*, or *17* haplotype, as compared with subjects with the reference haplotype (45–47). At the molecular level, these pharmacokinetic alterations may be largely explained by a decreased expression of functional OATP1B1 protein in the cell membrane, resulting from a sorting error (14,52,57).

On the other hand, two recent small studies suggest an "inverse" effect of the *SLCO1B1*1b* haplotype (i.e., c.388G allele) on pravastatin pharmacokinetics. Mwinyi *et al.* (46) reported that the AUC of pravastatin (after 40 mg) was about 35% lower in subjects carrying the *1b* haplotype (*1a/*1b* or *1b/*1b* genotype) than in subjects with the *1a/*1a* reference genotype (this difference did not reach statistical significance). Maeda *et al.* (59) found that the AUC of pravastatin (10 mg) was about 35% lower in Japanese subjects with the *1b/*1b* genotype as compared with the reference genotype. Thus, the results from these two studies are consistent. In contrast, the oral clearance of pravastatin was similar among Japanese subjects with the *1a/*1a* and *1b/*1b* genotypes (45).

We have recently carried out a small pilot trial to investigate whether the *SLCO1B1* polymorphism influences the pharmacokinetics and lipid-lowering efficacy of pravastatin during multiple dosing in healthy volunteers (60). In this prospective, parallel-group study, eight carriers of a *SLCO1B1* variant haplotype and eight controls received 40 mg pravastatin once daily for 3 weeks. The variant haplotype group included three heterozygous carriers of the *15*, four heterozygous carriers of the *17*, and one subject homozygous for the *17* haplotype. The subjects in the control group did not carry any of the haplotypes *5, *15, or *17. The mean AUC of pravastatin was about 110% higher and the mean peak concentration in plasma (C_{max}) was about 230% higher in the *SLCO1B1* variant haplotype group than in the control group (60) (Fig. 3). Thus, the *SLCO1B1* polymorphism seems to have a similar impact on the pharmacokinetics of single- and multiple-dose pravastatin.

The clear effect of the *SLCO1B1* polymorphism on the pharmacokinetics of pravastatin at steady-state (60) indicated that other uptake transporters located at the sinusoidal membrane of hepatocytes did not compensate to a significant degree for the reduced activity of OATP1B1. Theoretically, hepatocytes deficient in OATP1B1-mediated uptake transport might develop adaptive mechanisms such as compensatory up-regulation of another uptake transporter, but this does not seem to be the case considering the similar effects of the *SLCO1B1* polymorphism on the pharmacokinetics of single- and multiple-dose pravastatin (45–47,60). Interestingly, multiple OATP family members including OATP1B1, OATP1B3, and OATP2B1 have been shown to mediate the hepatic uptake of rosuvastatin (19,44). The major human hepatic bile acid uptake transporter, sodium-dependent taurocholate cotransporting polypeptide [NTCP (*SLC10A1*)], also transports rosuvastatin (44).

The elimination half-life of pravastatin was slightly but significantly increased in subjects with the *SLCO1B1*17* haplotype (47), which would be compatible with a reduced systemic clearance of pravastatin in subjects with impaired function of OATP1B1. OATP1B1-mediated uptake of pravastatin into the liver is a prerequisite as well as a rate-limiting step for its biliary elimination via MRP2 and possibly other hepatic efflux transporters. Once pravastatin gains access into hepatocytes, it does not undergo significant biotransformation, but is excreted unchanged into the bile (2,6). In this regard, the efflux transporters localized on the canalicular membrane of the hepatocyte represent the final step in the vectorial transport pathway of pravastatin from portal blood into bile (20,21,23,24) (Fig. 1). The notion that uptake transporters (such as OATP1B1) and efflux transporters (such as MRP2) may act in concert to facilitate detoxification of xenobiotics is supported by results from recent studies using double-transfected cell systems expressing both OATP1B1 and MRP2 (36,61). Indeed, this dynamic interplay between uptake and efflux transporters in various tissues probably plays an essential role in the drug disposition process (20).

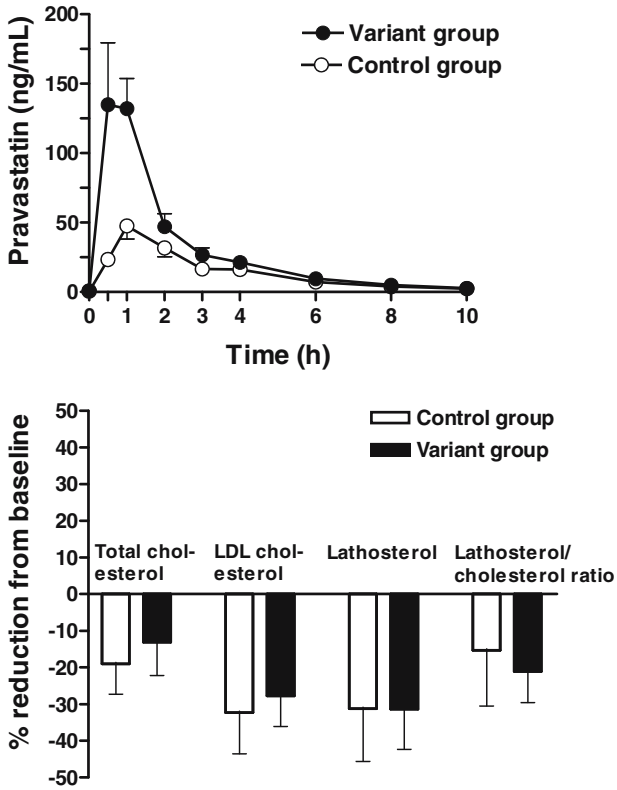

Fig. 3. Plasma pravastatin concentration–time profiles (*upper panel*; mean±SE) and lipid response (*lower panel*; mean±SD) in eight subjects with a *SLCO1B1* variant haplotype and in eight controls after treatment with 40 mg pravastatin daily for 3 weeks (see text for study design and characteristics of the subjects). Lathosterol is a late intermediate in the cholesterol synthesis pathway, and plasma lathosterol and the ratio of lathosterol to cholesterol in plasma are indicators of the activity of hepatic HMG-CoA reductase and the rate of total cholesterol synthesis *in vivo* (78,85–87) (reprinted from (60) with permission from the American Society for Clinical Pharmacology and Therapeutics).

MRP2

Absence of the MRP2 protein due to certain mutations in the *ABCC2* gene results in conjugated hyperbilirubinemia, the Dubin–Johnson syndrome (25,62). A large number of sequence variations have been described in the *ABCC2* gene, but little is currently known about the effects of genetic variation in *ABCC2* on the pharmacokinetics of drugs in humans. Impaired function of MRP2 might result in increased absorption and reduced biliary and/or urinary excretion of pravastatin, enhancing the systemic exposure to pravastatin. In rats, Mrp2 plays a major role in the biliary elimination of pravastatin, as demonstrated by the several-fold higher plasma pravastatin concentrations in Mrp2-deficient TR- rats after both oral and intravenous pravastatin administration (63).

In a recent study, the mean AUC and C_{max} of pravastatin were about 70% *lower* in three healthy volunteers who were heterozygous for the synonymous *ABCC2* c.1446C>G SNP than in 35 subjects not carrying this SNP (64). The effect of this SNP on MRP2 mRNA expression was investigated in about 90 human liver samples, and the mean mRNA expression was about 100% higher in livers with the c.1446CG genotype ($n=7$) than in the 86 livers with the reference genotype, c.1446CC (64). These findings support the idea that this SNP is associated with a reduced oral bioavailability of pravastatin as a consequence of increased MRP2 expression in the gut wall and/or liver. It remains to be clarified how this synonymous SNP could result in increased MRP2 expression. The effects of the *ABCC2* polymorphism on the pharmacokinetics of pravastatin and other MRP2 substrates warrant further study.

MDR1

Several SNPs have been found in the *ABCB1*/*MDR1* gene encoding the efflux transporter P-glycoprotein (65). Some of these SNPs appear to be associated with altered P-glycoprotein expression and function, although different studies have yielded conflicting results (65). We recently found no significant associations between the *ABCB1* polymorphism and the pharmacokinetics of pravastatin (47). These results are in line with the notion that P-glycoprotein does not play an important role in pravastatin disposition (see above).

Other Transporters

The possible effects of polymorphisms in the genes encoding OATP2B1 (*SLCO2B1*) and OAT3 (*SLC22A8*) on pravastatin disposition have been little investigated and merit further study (45,47,56). Zhang *et al.* (66) recently found an association between a frequent SNP in the gene encoding BCRP (*ABCG2*) (c.421C>A) and the pharmacokinetics of rosuvastatin in healthy Chinese males. The AUC of rosuvastatin after a single dose of 20 mg was about 80% higher in carriers of the c.421A variant allele as compared with subjects with the reference genotype (c.421CC). The possible effects of this polymorphism on the disposition of pravastatin, which also is a substrate of BCRP (30), remain to be investigated.

POSSIBLE CLINICAL CONSEQUENCES OF THE *SLCO1B1* POLYMORPHISM FOR PRAVASTATIN

Effectiveness of Pravastatin

There is significant interindividual variation in the lipid-lowering response to statin therapy, but the origins of this variation are still poorly understood (67–69). In a study in 56 patients with hypercholesterolemia treated with pravastatin, eight (14%) had a poor lipid-lowering response and three (5.4%) showed practically no response (70). A number of genetic polymorphisms have been reported to have an impact on response to statins, but few results have been replicated and most published studies have evaluated only one SNP at a time (67–69). In addition, the magnitude of the genetic effects found has been in most cases small (67–69,71,72).

Pravastatin and other statins reduce plasma concentrations of total and low-density lipoprotein (LDL) cholesterol primarily by inhibiting the rate-limiting enzyme of cholesterol synthesis, hepatic HMG-CoA reductase (73,74). It can be postulated that the increased plasma pravastatin concentrations observed in subjects with reduced activity of OATP1B1 are a result of diminished hepatic uptake of pravastatin (18). Therefore, subjects with an impaired OATP1B1-mediated pravastatin transport might exhibit reduced cholesterol-lowering efficacy due to lower intracellular pravastatin concentrations. Indeed, a retrospective study in 41 healthy white subjects suggested a smaller response to a single dose of pravastatin (40 mg) among carriers of the *SLCO1B1*17* haplotype in terms of inhibition of cholesterol synthesis (48). We recently carried out a prospective pilot study in healthy volunteers to further investigate this question (60). A 3-week treatment with pravastatin (40 mg/day) significantly reduced the concentration of total and LDL cholesterol in both the *SLCO1B1* variant haplotype group and the control group (see previous section for characteristics of the subjects) (Fig. 3). There was no significant difference in the lipid-lowering efficacy of pravastatin between the groups, despite considerably higher plasma pravastatin concentrations in carriers of a *SLCO1B1* variant haplotype (indirectly suggesting lower intrahepatic pravastatin concentrations). For example, the percentage reduction in LDL cholesterol from baseline was similar, about 30%, in both groups. LDL responses of a similar magnitude have been observed in clinical trials with the same pravastatin dose (40 mg/day) (73,75,76). Although our study had sufficient statistical power to detect only a large difference in lipid response between the two groups (60), the results suggest that the *SLCO1B1* polymorphism does not play a major role in non-response to pravastatin.

At first glance, the absence of a clear difference in the lipid-lowering efficacy of pravastatin between the variant *SLCO1B1* haplotype and control groups seems to be at odds with the pharmacokinetic results, showing increased systemic exposure to pravastatin in the subjects with variant *SLCO1B1* haplotypes (60). However, it appears that the dose–response curves for statins are steepest with doses below the lower limit of the recommended dose range (which is 10 mg/day for pravastatin), being shallow across their usual dose ranges (73,76,77). For example, clinical studies found

little difference in the LDL response to pravastatin between daily doses of 20 and 40 mg (75,76). Finally, it should be noted that the relationship between statin-induced intracellular inhibition of cholesterol synthesis and the cholesterol-lowering efficacy is rather complex (74,78–80).

In a recent retrospective study on elderly Japanese patients undergoing treatment with pravastatin, atorvastatin, or simvastatin, subjects with the *SLCO1B1* c.521TC genotype ($n=20$) showed a smaller mean percentage reduction in total cholesterol concentration (16.5%), as compared with those with the reference genotype, c.521TT (22.3%; $n=44$) ($P<0.05$) (81). The LDL response was also smaller among the c.521TC group (12.4 *versus* 29.0%; $P=0.094$). These findings are in line with the hypothesis that hepatic uptake of statins among subjects with the c.521TC genotype is impaired, resulting in a smaller lipid response. In contrast, the c.521T>C SNP was not associated with lipid-lowering response to pravastatin in a recent retrospective study involving 462 patients on pravastatin treatment (72). Further clinical studies are warranted to characterize the impact of the *SLCO1B1* polymorphism on the lipid response to pravastatin and other statins in patients with hypercholesterolemia.

Adverse Effects of Pravastatin

Pravastatin at a dosage of 40 mg/day has been shown to possess a very favourable tolerability profile in long-term clinical trials (82). However, because the myotoxic effects of statins are concentration-dependent (83), subjects with an impaired activity of OATP1B1 might be more susceptible to pravastatin-induced myopathy than subjects with a normal phenotype, as a result of elevated peripheral plasma pravastatin concentrations. Indeed, Morimoto *et al.* (84) reported that the frequency of the *SLCO1B1*15* haplotype was significantly higher in Japanese patients who experienced myopathy after receiving pravastatin or atorvastatin (which is also an OATP1B1 substrate) (14) than in patients without myopathy. From the pharmacokinetic point of view, the risk of pravastatin-induced myopathy with pravastatin 40 mg/day (the highest licensed dose) in carriers of *SLCO1B1* SNPs and haplotypes associated with impaired OATP1B1 activity would be expected to be similar to that during treatment with 60–80 mg pravastatin daily. The possible impact of the *SLCO1B1* polymorphism on the tolerability of pravastatin 40 mg/day merits further investigation.

CONCLUSION

The role of drug transporters in pravastatin disposition is underscored by the fact that pravastatin does not undergo significant CYP-mediated biotransformation (2,6). Pravastatin is a substrate for the hepatic uptake transporter OATP1B1 (12,13), and recent studies in Caucasian and Japanese subjects indicate that pravastatin plasma concentrations can be expected to be 50–100% higher in individuals carrying the *SLCO1B1* c.521C variant (45–47), as found in the **5*, **15*, **16*, and **17* haplotypes (49). Judging from the reported allele frequencies of functionally significant *SLCO1B1* SNPs and haplotypes in different ethnic groups (45,47,49,51,52), overall 2–5% of individuals in various populations may be expected to show markedly elevated plasma pravastatin concentrations. Importantly, the impact of the *SLCO1B1* polymorphism on different statins may be dependent on ethnicity (21). This is an issue that merits further investigation. Further, prospective studies with a sufficiently large number of subjects are necessary to better define the impact of the *SLCO1B1* polymorphism, especially the c.521T>C SNP, on the systemic exposure to pravastatin and other statins in different ethnic groups. There is preliminary evidence to suggest that the *SLCO1B1* polymorphism is not a major determinant of the lipid-lowering response to pravastatin (60,72). Several lines of evidence from *in vitro* and animal studies suggest a major role for the efflux transporter MRP2 in pravastatin disposition in humans [(63) and references therein]; however, few studies have so far investigated the impact of the *ABCC2* polymorphism on pravastatin pharmacokinetics (47,64). This is however not a simple task due to the complexity of the *ABCC2* gene. As it is, there remain unknown sources of variability in the pharmacokinetics and effects of pravastatin. The possible consequences of drug transporter polymorphisms, especially the *SLCO1B1* polymorphism, for the lipid-lowering efficacy and tolerability profile of pravastatin and other statins in various ethnic groups warrant further study.

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