Research Highlights

Individualizing statin therapy: beyond cytochrome P450

Statin therapy is a relatively safe and effective way to lower cholesterol levels, and with that, reduce morbidity and mortality [1]. However, response to statin therapy varies. Some patients have a lipid-lowering effect that is inadequate, and others develop adverse drug reactions, such as myopathy and rhabdomyolysis [2]. Many factors are involved in the variation in drug response. Better knowledge regarding these factors will result in the identification of patients with an inadequate response or patients who will develop adverse drug reactions prior to start of therapy. Individualization of statin therapy with alternative doses or alternative drugs will result in the improvement of the effectiveness and safety of statin therapy.

Factors that are involved in variation of statin response are the effects of genetic variation and the effects of co-prescribed drugs. Two regularly used statins, simvastatin and atorvastatin, are metabolized by the CYP3A4 enzyme to hydroxymetabolites [3,4]. The area under curve (AUC) of simvastatin increases five- to 20-fold if itraconazol, a potent CYP3A4 inhibitor, is co-prescribed, and the AUC of atorvastatin increases two- to four-fold [5]. The risk of myopathy with these statins is markedly increased if combined with drugs inhibiting CYP3A4 enzymes [5,6]. Although less well elucidated, genetic

variation in the *CYP3A4* gene also affects the metabolism of simvastatin and atorvastatin [7].

Of course, many more transporters and enzymes than just CYP3A4 are involved in the pharmacokinetics of statins. Knowledge on the role of transporters and enzymes is slowly being added to. Recently, in a genome-wide association (GWA) study, a strong association between a polymorphism in the *SLCO1B1* gene (*SLCO1B1**5) and severe statin-induced myopathy was identified [8]. The *SLCO1B1* gene encodes the organic anion transporting polypeptide 1B1 (OATP1B1), expressed at the basolateral membrane of hepatocytes. Genetic variation in the *SLCO1B1* gene impairs the uptake of substrates. The risk of myopathy was 17-times higher in homozygous carriers of the risk allele versus homozygous carriers of the nonrisk allele.

Statins can exist in acid form and in lactone form. Atorvastatin lactone is a pharmacologically inactive metabolite of atorvastatin, while simvastatin and pravastatin are given as lactones and metabolized to the pharmacologically active simvastatin acid and pravastatin acid, respectively. One of the complicating factors in studying the adverse drug reactions during statin therapy is that the cyclic lactones may be more myotoxic than the acid form of the statin [9,10]. The role of the acid and lactone form is analyzed separately in some studies.

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*SLCO1B1**5 polymorphism and mild side effects during statin therapy

Evaluation of: Voora D, Shah SH, Spasojevic I *et al.*: The *SLCO1B1**5 genetic variant is associated with statin-induced side effects. *J. Am. Coll. Cardiol.* 54(17), 1609–1616 (2009).

In the abovementioned GWA study by Link *et al.*, only severe cases of myopathy with increased creatine kinase (CK) levels

were included [8]. They found an association between the *SLCO1B1**5 polymorphism and severe myopathy. In clinical practice, statin-induced side effects are often not caused by increased CK levels, and cases of severe myopathy during statin therapy are rare. The incidence of mild side effects during statin therapy is estimated to be approximately 5–10% and results in many discontinuations.

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In the study by Voora *et al.*, the association between the *SLCO1B1**5 polymorphism and statin-induced myopathy was further elucidated [11]. Study participants were randomly assigned to simvastatin, atorvastatin or pravastatin therapy, with an 8-week low-dose treatment followed by an 8-week high-dose treatment. The composite end point was discontinuation in case of any side effects, myalgia or muscle cramps, or elevated CK levels. In this study, associations between genetic variation in the *CYP2D6*, *CYP2C8*, *CYP2C9*, *CYP3A4* and *SLCO1B1* genes and the occurrence of the composite end point was assessed. In a subgroup of patients, simvastatin acid, lactone, pravastatin acid and lactone concentrations were measured.

A total of 22% of the participants had at least one end point. Carriers of the *SLCO1B1**5 allele had a higher risk for adverse events (noncarriers: 19%; carriers of one allele: 27%; and carriers of two alleles: 50%). The effect was owing to the simvastatin and atorvastatin users; in the pravastatin users, no association was found between the number of *SLCO1B1**5 variant alleles and adverse events. If the

analyses were limited to those participants with adverse events but no elevated CK level, associations remained.

There was no difference between carriers and noncarriers of the *SLCO1B1**5 polymorphism in terms of low-density lipoprotein cholesterol reduction. There was a positive association between the *SLCO1B1**5 risk allele and simvastatin acid concentration during the high-dose period. No association was found for pravastatin.

From the GWA analyses, it was already known that *SLCO1B1**5 is associated with elevated CK level adverse events. This study adds to the fact that the association is also present for non-CK elevated adverse events. This effect was not found for pravastatin. Both simvastatin and pravastatin are substrates for OATP1B1 encoded by the *SLCO1B1* gene, making the differences hard to explain. The *SLCO1B1**5 polymorphism was associated with higher simvastatin acid levels, suggesting that simvastatin acid may mediate the side effects observed. The higher levels of simvastatin acid are contrary to the studies that indicate that the lactone form is more myotoxic than the acid form [9,10].

*SLCO1B1**5 polymorphism and the interaction between rifampicin and atorvastatin

Evaluation of: He YJ, Zhang W, Chen Y *et al.*: Rifampicin alters atorvastatin plasma concentration on the basis of *SLCO1B1* 521T>C polymorphism. *Clin. Chim. Acta* 405(1–2), 49–52 (2009).

Pravastatin and simvastatin acid concentrations are affected by *SLCO1B1* polymorphisms. Rifampicin alters the pharmacokinetics of atorvastatin on the level of CYP enzymes and on the level of hepatic transporters. Rifampicin inhibits the activity of OATP1B1 in humans, encoded by the *SLCO1B1* gene. In the study by He *et al.*, the impact of the *SLCO1B1**5 polymorphism on the interaction between atorvastatin and rifampicin was analyzed [12].

A total of 16 subjects were given, in random sequence, a single dose of atorvastatin plus rifampicin and a single dose of atorvastatin plus placebo with a 2-week wash-out period. This was followed by a single dose of rifampicin. Venous blood samples were collected and analyzed and the AUC from 0 to 48 h calculated. The change in atorvastatin pharmacokinetics with and without co-administration of rifampicin was analyzed.

Co-administration of rifampicin with simvastatin resulted in higher AUC_{0–48} for simvastatin. This increase was larger with the number of *SLCO1B1**5 wild-type alleles. The increase in AUC_{0–48} value was nearly tripled in participants homozygous for the wild-type *SLCO1B1**5 genotype

compared with participants homozygous for the *SLCO1B1**5 variant allele. Also, the percentage decrease in half-life and clearance divided by the bioavailability were influenced.

No differences in the pharmacokinetics of rifampicin were found between *SLCO1B1**5 genotypes, and therefore, the differences in atorvastatin AUCs cannot be explained by the effect on the pharmacokinetics of rifampicin.

Apparently, the *SLCO1B1* genotype has an important role in the interaction between rifampicin and atorvastatin. Rifampicin's interaction with atorvastatin mimics the effect of the *SLCO1B1* genotype, and rifampicin may increase the risk of myopathy.

Statin myotoxicity, UGT and the acid and lactone form

Evaluation of: Riedmaier S, Klein K, Hofmann U *et al.*: UDP-glucuronosyltransferase (UGT) polymorphisms affect atorvastatin lactonization *in vitro* and *in vivo*. *Clin. Pharmacol. Ther.* 87(1), 65–73 (2009).

It is suggested that the lactone form of statins are more myotoxic than the acid form. Atorvastatin-treated patients experiencing atorvastatin-related myopathy demonstrated two- to three-fold higher plasma concentrations of atorvastatin lactone and certain metabolites, including CYP3A-formed hydroxylated metabolites, but no change in the level of atorvastatin itself [9]. In a cellular myotoxicity model, lactones have been demonstrated to be more cytotoxic than the corresponding acids [10]. However, this association is not well established.

Atorvastatin was given as atorvastatin acid. Atorvastatin lactonization may occur both nonenzymatically at low intestinal pH and enzymatically through an unstable acyl glucuronide or a coenzyme A intermediate. Glucuronidation of atorvastatin is catalyzed by the UDP-glucuronyltransferases (UGTs) UGT1A1 and UGT1A3. In the study by Riedmaier *et al.*, the role of interindividual UGT variation and polymorphism in the formation of statin lactones has been studied both *in vitro* and *in vivo* [13].

In vitro, atorvastatin lactonization was correlated with the amount of UGT1A3 protein and mRNA, and not with the amount of UGT1A1 protein and mRNA. This indicates that UGT1A3 is the major isoenzyme catalyzing atorvastatin lactonization in human liver microsomes. The authors tested whether *UGT1A1*28*

has an association with atorvastatin lactonization, and, surprisingly they found a strong association. This unexpected finding could be explained by linkage disequilibrium between *UGT1A1*28* and genetic variation in *UGT1A3*. *UGT1A3*2* was significantly associated with the amount of UGT1A3 mRNA, protein and atorvastatin lactonization.

A total of 56 volunteers, who had received single-dose atorvastatin in previous studies, were genotyped for *UGT1A3*. Significant associations were found between *UGT1A3*2* and atorvastatin lactone/acid $AUC_{0-\infty}$, between *UGT1A3*2* and 2-hydroxyatorvastatin lactone/acid $AUC_{0-\infty}$ and between *UGT1A3*2* and 2-hydroxyatorvastatin lactone $AUC_{0-\infty}$. No associations were found with atorvastatin lactone $AUC_{0-\infty}$ or atorvastatin acid $AUC_{0-\infty}$.

The data of this study suggest that genetic variation in *UGT1A3* is a candidate gene that influences atorvastatin toxicity, since UGT1A3 is associated with atorvastatin lactonization and atorvastatin lactone is associated with toxicity. The association between genetic variation in *UGT1A3* and atorvastatin lactonization was found both in human liver microsomes and in atorvastatin-treated volunteers.

From these three studies, it can be concluded that both *SLCO1B1* and *UGT1A3* may play an important role in the response to statin therapy. However, their exact roles still need to be clarified before they can be used in clinical practice. The results on the role of the acid and lactone forms are interesting although, at this time, contradictory. Overall, response to statin therapy is an interesting topic for further research.

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