Genome Medicine

Review

Pharmacogenomic insights into treatment and management of statin-induced myopathy

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Abstract

Although statins are generally well tolerated, the most common adverse drug reaction from statin therapy is myopathy. This article reviews the current pharmacogenomic knowledge of statin-induced myopathy. Furthermore, we will discuss the importance of recent pharmacogenetic advances for the treatment and management of statin-induced myopathy. Variation in the *SLCO1B1* gene is associated with increased incidence of statin-induced myopathy, particularly with simvastatin and less so with other statins. If different pharmacokinetic enzymes and transporters are responsible for susceptibility to myopathy, this may explain differences in the occurrence of statin-induced myopathy in individual patients. Genotyping in patients suffering from statin-induced myopathy may help to personalize the choice of statin for the lowest chance of developing myopathy.

Introduction

To reduce the morbidity and mortality associated with heart disease, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins) are used by millions of patients worldwide. The primary mechanism by which statins reduce the risk of coronary artery disease (CAD) involves lowering low-density lipoprotein cholesterol (LDLc) in plasma. Although generally well tolerated, the most common adverse drug reaction (ADR) from statin therapy is myopathy, symptoms of which can range from myalgia (mild fatigue and muscle pain without raised creatine kinase (CK) [1]) to life-threatening rhabdomyolysis (muscle symptoms associated with marked CK elevations, typically substantially more than ten times the upper limit of normal [1]). Among 20 randomized trials, the incidence of minor muscle pains was 190 per 100,000 person years, whereas rhabdomyolysis incidence was reported to be 1.6 per 100,000 person years [2]. In the ambulatory setting, the incidence of hospitalized rhabdomyolysis per 100,000 person years for monotherapy with atorvastatin, pravastatin, or simvastatin was shown to be 4.4 [3]. In contrast to the incidence of minor muscle pains in clinical trials, observational studies have reported considerably higher numbers of statin-associated myalgia cases [4,5].

Currently, there is no consensus of the exact definition of statin-induced myopathy (SIM) [6]. The mechanism behind SIM is poorly understood, but a number of (arguable) underlying mechanisms have been proposed, including isoprenoid and coenzyme Q10 depletion, low cholesterol content, myocyte skeletal membrane-related instability, and mitochondrial dysfunction. SIM is of great clinical importance because (i) mild ADRs in patients on lifelong statin treatment lower the quality of life, and (ii) patients may discontinue statin therapy because of intolerance.

Numerous factors have been proposed that may increase the risk of SIM, including older age, female sex, low body mass index, excessive alcohol use, and drug interactions (for example, concomitant use of fibrates, ciclosporin, protease inhibitors, macrolide antibiotics, and amiodarone) [6]. Recent advances in pharmacogenomic research have revealed important genetic factors that contribute to the risk of ADRs. Clinically important examples of gene-drug interactions are (i) coumarins, genetic variation in *VKORC1*, *CYP2C9*, and the risk of bleeding, (ii) abacavir, *HLA-B**5701, and hypersensitivity, and (iii) irinotecan, *UGT1A1**28 and neutropenia. This article reviews the current pharmacogenomic knowledge of SIM. Furthermore, we will discuss the importance of recent pharmacogenetic advances for the treatment and management of SIM.

Genetic predisposition to statin-induced myopathy

Several studies have been conducted to investigate the contribution of genetic variability to the risk of SIM. Pharmacokinetically related genes are obvious candidates, since the exposure to a particular statin is much higher for a patient who is a poor metabolizer for a certain

ADR, adverse drug reaction; CK, creatine kinase; CPT, carnitine palmitoyltransferase; CYP, cytochrome P-450; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; SIM, statin-induced myopathy; SNP, single nucleotide polymorphism.

cytochrome P-450 (CYP) enzyme, compared to an intermediate, extensive or rapid metabolizer. For example, the pharmacokinetics of fluvastatin depend on the *CYP2C9* genotype, with a three-fold difference in the active enantiomer and an even greater difference in the inactive enantiomer [7]. A case report in 2004/2005 suggested genetic variability within the *CYP2C8* gene to be causative of a case of rhabdomyolysis associated with cerivastatin (withdrawn from market) [8,9]. The relationship between *CYP3A4* and *CYP3A5* gene polymorphisms and atorvastatin-induced muscle damage was investigated in a case-control study with 68 cases and 69 controls [10]. Muscle damage (measured as degree of serum CK elevation) was greatest in patients on atorvastatin treatment and homozygous for the *CYP3A5**3 allele. Another study, including 136 patients with SIM (taking either atorvastatin or simvastatin) and 296 controls, investigated the relationship between 388 common single nucleotide polymorphisms (SNPs; most of them within CYP-coding genes) and elevated CK or myalgia, and reported an association between the *CYP2D6**4 allele and atorvastatin-induced myopathy [11]. Interestingly, the results extended to muscle events induced by simvastatin, which is not known to be metabolized by CYP2D6.

Drug transporters that mediate the uptake and elimination of statins have recently gained interest. The hepatocellular influx transporter OATP1B1 (encoded by the *SLCO1B1* gene) and intestinal and hepatocellular efflux transporter ABCB1 (*ABCB1* gene) have been shown to affect the pharmacokinetics of statins [12-14].

The pharmacokinetically different profile of statins between *SLCO1B1* genotypes has also been shown to affect the risk of myopathy. The SEARCH Collaborative Group study conducted a genome-wide association study in 85 myopathy cases and 90 controls who were all taking 80 mg of simvastatin once daily [15]. Only a non-coding SNP (rs4363657) within the *SLCO1B1* gene showed a strong association with myopathy. This SNP is in strong linkage disequilibrium with the non-synonymous rs4149056 SNP, which had previously been associated with altered statin pharmacokinetics [13,14]. For each copy of the variant allele, there was approximately a four times higher risk of myopathy. Importantly, this finding was replicated in a trial with subjects treated with 40 mg simvastatin once daily [15]. The STRENGTH study investigated the genetics of four *CYP* genes and the *SLCO1B1* gene in relation to SIM (use of simvastatin, atorvastatin and pravastatin was included). Not only did the study confirm the findings from the SEARCH study, it also reported an association between the *SLCO1B1* risk allele and myalgia symptoms without CK elevation for simvastatin and atorvastatin (weaker), but not for pravastatin treatment [16].

An additional potentially important, but very rare, SNP in the *SLCO1B1* gene is 1628T>G. This novel mutation was discovered by a Japanese group in a patient with pravastatin-induced myopathy [17], and was shown to reduce transporter activity of OATP1B1 [18]. In another study, the TTT (or TAT) haplotype of the *ABCB1* 1236C>T, 2677G>A/T, or 3435C>T polymorphisms was more frequently seen in the simvastatin-treated group without myalgia [19]. This observation may seem surprising, as simvastatin (acid) area under the plasma-concentration-time curve has been shown to be 60% higher among homozygous haplotype *ABCB1 TTT* carriers [12].

Underlying disease in statin-induced myopathy

Several underlying diseases may increase the risk of developing myopathy during statin therapy. These diseases include exercise intolerance disorders (such as McArdle disease or carnitine palmitoyltransferase (CPT) II deficiency), malignant hyperthermia, coenzyme Q10 deficiency, and gene-expression abnormalities (such as overexpression of major histocompatibility complex class I (MHC-I)) [20]. The evidence that these diseases lead to an increased risk of myopathy in combination with statin use is not always clear. However, for example, McArdle disease and CPT II deficiency have been shown to be more common in statin myopathy patients [21]. Both disorders are very rare (prevalence of McArdle 1:100,000 individuals [22], and CPT II deficiency 1:300,000 individuals [21]). These genetic or acquired diseases might be asymptomatic in patients starting statin therapy, and statins may then act as unmasking agents [23]. These underlying diseases might therefore be one reason why certain patients develop myopathy during statin use. However, because of the rarity of the diseases, it does not seem appropriate to test patients for these diseases before initiating statin use. If serum CK is still high after discontinuation of statins, the physician should pursue further diagnostic evaluations for the detection of neuromuscular disorders [23].

New insights into treatment and management

With the increasing number of patients being treated with (high-dose) statins to meet the stringent cholesterol levels as advocated in (inter)national guidelines, SIM becomes more common in absolute numbers. Clinically, mild myopathic symptoms may lead to poor adherence to statin treatment and lower clinical benefit, and extreme myopathy manifests as the rare but life-threatening event rhabdomyolysis. Therefore, it is also important to evaluate the role of pharmacogenetic interactions in the prediction of the more common myalgia. This is a scientific challenge because of the difficulty of defining the phenotype, but is very valuable because the incidence of myalgia complaints is relatively high among statin users.

Besides genetics, other considerations should be taken into account when prescribing statins. For example, female sex was shown to be a risk factor for developing adverse effects during statin therapy [16]. This may be due to the fact that

the body weight of females is lower than that of males, and therefore lower doses for females should be considered [16]. It is also of utmost importance that the use of other drugs by the patient is considered. Patients that use CYP3A4 inhibitors (such as fibrates, protease inhibitors, amiodarone, and ciclosporin) should not use simvastatin, but should preferably be treated with a statin that is metabolized by other enzymes (such as fluvastatin or atorvastatin) [24].

Methodological issues in pharmacogenomics

In this review, we have given an overview of the studies that aimed to unravel the contribution of genetic variability to the risk of SIM. Before addressing the clinical implications of these findings, it is important to note that there seems to be a common pattern of (pharmaco) genomic associations that cannot be confirmed by others [25]. Reasons for inconsistent findings between studies include differences in study population, different outcome definitions, statistical power issues, and chance findings due to testing many genetic variables. Many studies have been published that examine genetic markers for the prediction of statin efficacy [26]. However, very few genetic interactions have been confirmed, and the clinical utility of the interactions is very low, because the differential efficacy caused by genes is small [26]. With this in mind, the current evidence is most compelling for the *SLCO1B1* gene since this association has been confirmed in different studies [15,16] and the findings are corroborated by previously conducted genetic pharmacokinetic studies [14]. However, variation in other pharmacokinetic enzymes/drug transporters might also be of importance for one or more statins, and therefore statin-specific studies should be conducted to confirm these findings as well. It would be helpful for this process if the complete metabolic route for all statins were elucidated, but unfortunately this is not the case; the pathway is very complex and involves numerous transporters, CYP450 enzymes, and phase II enzymes.

Implications for clinical practice

The robust association between the *SLCO1B1* gene and SIM may warrant genetic testing in clinical practice, since it is increasingly clear that there might be an important genetic component in the prediction of the development of SIM during statin treatment. However, it is important to realize that there are significant differences between the statins concerning their route of hepatic uptake. Lipophilic statins such as fluvastatin can enter the liver via passive diffusion, while hydrophilic statins need active transportation. Importantly, fluvastatin has been shown to have a pharmacokinetic profile independent of *SLCO1B1* genotype [27]. In studies investigating the pharmacogenetics of SIM, simvastatin (and to a lesser extent atorvastatin) seems to be an important substrate for the OATP1B1 transporter. Patients with the rs4149056 polymorphism in the *SLCO1B1* gene should therefore preferably be treated with another statin (such as fluvastatin). Because there are differences in pharmacokinetics and in susceptibility for drug transporters between statins, the genetic variation predicting the side-effects of these drugs might be different for each type of statin. Genotyping all patients before initiating therapy is not cost-effective at present because the risk of developing severe side-effects such as myopathy and rhabdomyolysis is low, but genotyping costs will probably decrease with time, changing the situation. In the future, genotyping before the start of therapy could be helpful in choosing the right statin for the individual patient, in such a way that the patient has a very low chance of developing SIM.

Competing interests

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Authors' contributions

Bas Peters and Anke-Hilse Maitland-van der Zee drafted the article. Anthonius de Boer, Olaf Klungel, and Frank Visseren reviewed and approved it for submission.

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