Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: informahealthcare.com/journals/iann20

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To cite this article: Cesare R. Sirtori, Giuliana Mombelli, Michela Triolo & Reijo Laaksonen (2012) Clinical response to statins: Mechanism(s) of variable activity and adverse effects, Annals of Medicine, 44:5, 419-432, DOI: 10.3109/07853890.2011.582135

To link to this article: https://doi.org/10.3109/07853890.2011.582135

Annals of Medicine, 2012; 44: 419–432

informa
healthcare

REVIEW ARTICLE

Clinical response to statins: Mechanism(s) of variable activity and adverse effects

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Abstract
Statins represent a major advance in the treatment of hypercholesterolemia, a significant risk factor for atherosclerosis. There is, however, notable interindividual variation in the cholesterolemic response to statins, and the origin of this variability is poorly understood; pharmacogenetics has attempted to determine the role of genetic factors. Myopathy, further, has been reported in a considerable percentage of patients, but the mechanisms underlying muscle injury have yet to be fully characterized. Most statins are the substrates of several cytochrome P450s (CYP). CYP polymorphisms may be responsible for variations in hypolipidemic activity; inhibitors of CYPs, e.g. of CYP3A4, can significantly raise plasma concentrations of several statins, but consequences in terms of clinical efficacy are not uniform. Pravastatin and rosuvastatin are not susceptible to CYP inhibition but are substrates of the organic anion-transporting polypeptide (OATP) 1B1, encoded by the SLCO1B1 gene. Essentially all statins are, in fact, substrates of membrane transporters: SLCO1B1 polymorphisms can decrease the liver uptake, as well as the therapeutic potential of these agents, and may be linked to their muscular side-effects. A better understanding of the mechanisms of statin handling will help to minimize adverse effects and interactions, as well as to improve their lipid-lowering efficiency.

Key words: *Cholesterolemic response, CYP450, genetic factors, muscular side-effects, SLCO1B1, statins*

Introduction

Clinical use of statins has grown to very extensive levels because of the efficacy of these oral agents in the management of hypercholesterolemia. In addition, the so-called pleiotropic effects (1,2) may provide additional benefit to statin users. Thus, the very wide use of these agents allows a large number of patients (estimated number in the world is around 200 million) to get benefit in terms of biochemical effects and cardiovascular risk reduction (3).

The efficacy of statin treatment may be reduced occasionally, because in some patients the biochemical response to treatment may be inadequate, e.g. for genetic reasons. In addition, in a relatively large number of patients compliance may be an issue due to side-effects such as myalgia and muscle weakness. Furthermore, reduced compliance may lead to reduced effects on both plasma lipids and clinical outcome as shown in the WOSCOPS Study: patients with no lipid-lowering experienced also no event reduction (4).

This review will focus on both aspects of statin treatment. The *variable cholesterol-lowering response* in some individuals appears to be related to genetic factors involving the target enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCoA), different steps regulating lipid metabolism, as well as variability of lipoprotein structure and composition. As yet, indications that these genetic polymorphisms affecting efficiency of statins may be associated with the cardiovascular risk are scarce and based only on a limited number of reports.

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(Received 23 October 2010; accepted 11 April 2011)

ISSN 0785-3890 print/ISSN 1365-2060 online © 2012 Informa UK, Ltd.
DOI: 10.3109/07853890.2011.582135

Key messages

- Genetic factors seem to affect the lipid-lowering efficacy of statins. However, we will have to await results from systematic large-scale studies before clinically useful genetic tests can be developed to predict treatment efficacy.
- Mild muscle toxicity is frequently observed in statin-treated patients; genetic tests can potentially be used to predict muscle side-effects, particularly in patients prescribed high doses of statins.

Abbreviations

ABCB	ATP-binding cassette subfamily
ALT	alanine aminotransferase
AUC	area under the curve
CETP	cholesteryl ester transfer protein
CK	creatine phosphokinase
CYP	cytochrome P450
EM	extensive metabolizer
HDL	high-density lipoprotein
HMGCoA	3-hydroxy-3-methylglutaryl-coenzyme A
LDL-C	low-density lipoprotein cholesterol
MHC	major histocompatibility complex class
MI	myocardial infarction
NPC1L1	Niemann–Pick C1-like 1
OATP	organic anion-transporting polypeptide
OR	odds ratio
PGC-1α	PPARgamma coactivator-1alpha
PM	poor metabolizer
SNP	single nucleotide polymorphism
TG	triglyceride
ULN	upper limits of normal
UM	ultrarapid metabolizer
VLDL	very-low-density lipoprotein

Statin-induced myalgia is most often unrelated to clinical or biochemical patterns such as changes in serum creatine phosphokinase (CK) and can involve 20% or more of treated patients, resulting in poor compliance (5). While waiting for the results of ongoing studies, involving sophisticated tests, allowing to predict better which individuals are at risk of developing muscle side-effects, it seemed worth the effort to evaluate the pharmacological basis of statin-induced muscular adverse effects, as well as the present knowledge on gene polymorphisms associated with muscle pain.

In order to assess properly the completeness of data retrieval we performed a PubMed and EMBASE search with the following key words: 'statins lipid lowering activity' (412 references in PubMed), 'statins lipid lowering genetics' (390 references), 'statin myopathy mechanisms' (56 references), and 'statin myopathy genetics' (73 references). The search was restricted to English-language journals published from January 2001 to December 2010, with some very recent additions.

Interindividual variability in the magnitude of response to statins: impact of genetics

The magnitude of response to treatment, even with the same dose of the same statin, may vary 10%–50% (6). This may pose an important clinical problem, since so far there is no reliable test to identify 'good' and 'poor' responders to a particular statin. A number of genetic polymorphisms have been evaluated in several clinical trials. Single nucleotide polymorphisms (SNPs) have been examined in some 30 different genes (7).

Genetic factors affecting statin activity

P450s

Most statins are metabolized by the P450 system, allowing these mainly lipophilic drugs to be transformed into hydrophilic molecules, to be disposed of by the kidneys. Exceptions to this general rule are pravastatin and rosuvastatin, hydrophilic molecules undergoing minimal metabolic handling. Metabolic transformations of statins may explain the variable cholesterol-lowering activity to a relatively modest extent, and genetic association findings related to activity should be tempered by the inadequate reports, so far, of clear pharmacokinetic changes. A good case in point is that of fluvastatin: polymorphisms of CYP2C9 appear to be associated with the kinetic behavior. Carriers of the variants Arg144Cys (*2) and Ile359Leu (*3) show increased areas under the curve (AUC) for the active enantiomer (8). However, the CYP2C9 variant with the highest AUCs paradoxically was associated with a reduced lipid-lowering efficacy.

With these reservations, differences in lipid responses have been detected for several statins metabolized by CYP450 enzymes. The effect of a CYP450-mediated metabolism (9) has been recorded in patients on atorvastatin. The promoter (A-290G) and non-synonymous polymorphism M445T in the CYP3A4 gene locus appear to be associated with lipid responses (9). In patients treated with 10 mg/day, the A-290G variant carriers had a reduced response (LDL-C $-31\% \pm 14\%$ versus $-37\% \pm 10\%$ for the whole sample), whereas the M445T variant carriers showed a modestly enhanced response (LDL-C $-40\% \pm 14\%$) (9). Atorvastatin is also metabolized by CYP3A5: the most common SNP A6986G (CYP3A5*3) was

associated with reduced cholesterol-lowering in non-African individuals (10). A prior study in 46 Europeans had noted instead a more marked LDL-C reduction in carriers of the same genotype after 1 year of treatment with lovastatin, simvastatin, or atorvastatin (11).

The effect of the common polymorphisms of the CYP2D6 gene might be of interest, in view of the high frequency of reduced activity variants. Poor metabolizers (PM) make up not less than 10% in most general populations, and a similar percentage occurs for the ultrarapid metabolizer (UM) status. An earlier report (12), investigating the CYP2D6 polymorphisms in terms of simvastatin-induced cholesterol reduction, demonstrated a higher efficacy in patients with low activity variants, and this finding was replicated in a study of ours (13). A pharmacogenetic investigation on the CYP2D6 variants on the efficacy and tolerability of simvastatin, reporting a moderately elevated hypocholesterolemic activity and a higher incidence of side-effects in PM with a lower efficacy in carriers of gene multiplications (14), was bitterly criticized (15). At present there appears to be no evidence of an involvement of CYP2D6 in statin metabolism, and the exact role of CYP2D6 on the lipid-lowering efficacy remains unclear. Simvastatin, like most statins, is in fact metabolized by CYP3A, and metabolic transformations mediated by this cytochrome are definitely more relevant (16), being frequently affected also by concomitant drug treatments (17).

Pravastatin, rosuvastatin, and pitavastatin undergo minimal CYP-mediated metabolism and are not generally susceptible to CYP inhibition, although some authors suggest that CYP2C9 may play a minor role in rosuvastatin metabolism after its rapid and selective liver uptake by the organic anion transporter protein (OATP) 1B1 (SLCO1B1 gene) (18). This does not exclude the possibility of potential drug interactions, e.g. with compounds inhibiting CYP2C9 activity, that may increase the AUC and thus affect also the lipid-lowering activity. An extensive overview on the role of CYPs in statin handling and the significance of drug interactions has been recently provided by Neuvonen (19).

Cellular transfer systems

An area of growing interest is that of energy and non-energy-mediated cellular transfer systems. The *ATP-binding cassette subfamily B (ABCB)*, responsible for the liver drug efflux and potentially influencing the lipid-lowering activity of statins, has received particular attention. In the case of simvastatin and fluvastatin, ABCB1 variants are associated to significant changes in drug responses. Carriers of the 1236T variant (rs11285030) showed a greater reduction in total and LDL-C after simvastatin; similar results were also observed for the 2677 G>A/T polymorphism (rs2032582), whereas a lower effect was noted in carriers of the 3435 G>T (rs1045642) (20). Berchovich et al. (21) observed a raised hypocholesterolemic response to fluvastatin in carriers of the haplotypes CETP H-13 GAAGA and MDR1-h4 GCCTA (21). Peters et al. (22) examined recently, in a group of 688 MI patients and 1,217 controls, the genetic variability of the ABCB1 gene versus the efficacy of statins in preventing myocardial infarction (MI). By testing 24 tagging SNPs, two SNPs (rs3789244AA, $P = 0.01$ and rs1922242AT, $P = 0.01$) were found to be associated with a significantly better preventive effect (odds ratios 0.39 and 0.23, respectively). Interestingly these SNPs were not reported to affect the lipid-lowering response of simvastatin in the previously mentioned study (20).

Kajinami et al. (23) studied the polymorphisms in the ABCG5/ABCG8 transporters, located in the liver plasma membranes, that mediate cholesterol excretion into bile. Rare mutations cause sitosterolemia, an inherited disorder characterized by hyperabsorption/reduced excretion of plant sterols (24). Among a number of evaluated polymorphisms in patients treated with atorvastatin 10 mg, the ABCG8 H19 allele was associated with a greater LDL-C reduction compared to the wild type (39.6 versus 36.6%; $P = 0.043$). The difference was further enhanced in non-carriers of a promoter variant of CY7A1 (42.7 versus 38.2%; $P = 0.048$) (23). This last finding is consistent with an earlier report by Pullinger et al. (25), who noted remarkable resistance to the lipid-lowering effects of statins in individuals with total loss of CYP7A1 activity.

A recent growing interest has been devoted to the ABCG2 efflux transporter, initially labeled as breast cancer resistance protein (BCRP) (26). A polymorphism of this ubiquitous transporter was evaluated by Keskitalo et al. (27), who reported that the AUC of atorvastatin increased by 72%, and that of rosuvastatin by 144%, in individuals with the ABCG2 c.421AA genotype as compared with the c.421CC genotype. The impact of the variant polymorphism on statin activity has been generally modest (26) with the exception of the case of rosuvastatin. In this case a very recent study in the Chinese population reported significantly better LDL-C reductions in the ABCG2 c.421AA carriers after 10 mg rosuvastatin (−58.4% versus −47.6% for the CC carriers) (28). Confirmatory findings have been more recently provided in a Caucasian population (29).

In the case of *non-energy-dependent influx regulators*, a number of reports have clearly shown that variants of the solute carrier OATP family, coded by the SLCO1B1 gene, may directly influence the lipid-lowering activity, besides their potential effects on myalgia (see below). The protein product OATP1B and its variants are directly associated with the LDL-C-lowering potency of, particularly, fluvastatin. For example, in the CC homozygous carriers of the 463C > A genotype (systematically associated with the 388A > G SNP) treated with fluvastatin, a mean LDL-C reduction of −31.5% ± 16.4% was recorded, whereas the same treatment led to more substantial reduction (−41% ± 14.2%) in AA homozygotes (30). A similar study with pravastatin, evaluating different genotypes, failed to detect significant differences in the lipid-lowering efficacy (31). However, in *pediatric patients with familial hypercholesterolemia*, as well as in pediatric cardiac transplant patients, a lower efficacy of pravastatin was observed in children with the 521TC genotype versus those with the 521TT reference genotype (−7.7% ± 7.7% LDL-C for the rare variant versus −33.5% ± 20.8% for the common 521 TT genotype) (32). Similar results were found in another investigation on pravastatin, atorvastatin, and simvastatin: hypercholesterolemic adult carriers of the 521C allele showed an attenuated total cholesterol-lowering effect, compared with TT homozygotes (−16.5% ± 10.5% versus −22.3% ± 8.7%; $P < 0.05$) (33). Interestingly, in the previously quoted report by Peters at al. (22) on the potential association between gene polymorphisms and MI prevention in statin-treated subjects, the odds ratio (OR) for a MI in subjects homozygous for the haplotype SLCO1B1*1A was 0.49 (95% CI 0.34–0.71) while it was 0.31 (95% CI 0.24–0.41) in heterozygotes or non-carriers of the **1A* haplotype. Somewhat paradoxically, the two SNPs previously shown to be associated with improved cholesterol reductions, i.e. 388A > G and 521T > C, were not found to affect the statin-mediated MI prevention.

Finally, Polisecki et al. (34) evaluated the effects of the genetic variants of the Niemann–Pick C1-like 1 (NPC1L1) gene (34). NPC1L1 plays a critical role in intestinal cholesterol absorption and is the target of action of ezetimibe (35) and phytosterols (36). The authors examined five variants of the gene in 5,804 elderly participants in the PROSPER study, randomized to either pravastatin 40 mg or placebo. Among the five variants, the −133A > G genotype was associated with the most marked variability on the LDL response, but with remarkable sex differences. Women with the AA genotype had the best response (−37.5% versus −34.5% for the GG carriers), the opposite occurring in men (-35.5% for the AA versus −38.8% for the GG). Interestingly, the minor alleles of the other four evaluated variants showed higher cholesterolemias and a higher incidence of cardiovascular events (34).

Cholesteryl ester transfer protein (CETP)

A well characterized association between statin response and genetic variability has been described for the cholesteryl ester transfer protein (CETP). CETP participates in reverse cholesterol transport by facilitating the transfer/exchange of cholesteryl esters from high-density lipoproteins (HDL) to very-low-density lipoproteins (VLDL) and to LDL, to be transported back to the liver.

A frequent polymorphism in the first intron of the CETP gene is referred to as *Taq*IB. Carriers of the B1 restriction site have higher plasma levels of CETP and lower plasma HDL-cholesterol (37). In the Regression Growth Evaluation Statin Study (REGRESS), it was observed that B2B2 carriers had a poor hypolipidemic response to pravastatin, but despite an inadequate lipid response a decreased coronary stenosis progression was recorded (38). More recently, however, a 10-year follow-up of REGRESS indicated that the *Taq*IB B2B2 carriers, in spite of the higher HDL-cholesterol, showed a significantly higher hazard ratio for atherosclerotic disease death (HR 1.59; $P = 001$), ischemic heart disease death (HR 1.53; $P = 0.03$), and all-cause mortality (HR 1.30; $P = 004$) (39). These findings confirm the earlier meta-analysis by Boekholdt et al. (40) from seven large clinical trials. In this, the *Taq*IB gene polymorphism was significantly associated with the risk of CVD in B2B2 subjects. However, additional adjustment for HDL-C levels reduced the statistical significance.

In another study in type 2 diabetics, atorvastatin treatment raised HDL-C levels by 8.4% in B1B1 carriers, whereas it had no effect on HDL-C in the B2B2 carriers, suggesting that the *Taq*IB polymorphism may modulate the effect of statins (41). Conversely there was no evidence for an impact of the *Taq*IB polymorphism on the cholesterol response to pravastatin. Another important polymorphism, described by Dutch investigators as the −659A, was found to be associated with increased HDL-C and also raised cardiovascular risk (42); no evidence for an association with lipid responses to statins has been reported (43).

Finally, the potential interaction between *CETP gene variability* and lipid-altering efficacy of statins was studied in patients receiving pravastatin, atorvastatin, or cerivastatin (44). This analysis focused on CETP haplotypes, including SNPs1-9 (TTCAAAGGG) and the smaller haplotypes SNPs4-9 (AAAGGG) and SNPs1-6 (TTCAAA). The authors observed that the

TTCAAA haplotype showed a gene–dose effect in predicting the HDL-cholesterol rise, whereas the TTCAAAGGG and AAAGGG haplotypes were associated with the triglyceride (TG)-lowering potency ($P < 0.04$ for both) (44).

Impact of apolipoprotein variants

A large number of studies have investigated particularly the role of the *apolipoprotein E* gene on lipid responses to statins. The human apoE gene is defined by three alleles, E2, E3, and E4, with increasing affinity for the LDL receptor (45). Lipoproteins containing the apoE4 isoform exert a more pronounced down-regulation of hepatic cholesterol synthesis, whereas E2-containing lipoproteins reduce plasma clearance with consequently increased LDL receptor activity. Therefore, statins may be less effective in reducing cholesterolemia in the apoE4 carriers (46,47), since they have a reduced LDL receptor load. Conversely, patients with the apoE2 genotype generally show a better response to statins (48,49). More recent studies have suggested that the relationship between the apoE genotype and cholesterol-lowering may be sex-specific, since a larger reduction of LDL-C was observed in male E2 carriers versus females (50). Interestingly, a reduced therapeutic compliance was reported in E4 homozygotes, possibly explained by the reduced therapeutic efficacy in some of these individuals (51). However, it should be underlined that E4 carriers may have a mostly reduced lipid-lowering efficacy but, as shown in a sub-study of the 4S trial, they gain remarkable benefit from simvastatin treatment (mortality risk 0.33 versus 0.66 for non-carriers) (52). Similarly, in the REGRESS study with pravastatin, E4 carriers had the least benefit in terms of LDL/HDL ratios (-0.040 versus 0.60 for the E2 carriers), but the E2 carriers had the least benefit in terms of angiographic parameters (53). These paradoxical findings may point to a 'pleiotropic' effect of statins on the reported stimulatory effects of E4 on, e.g., macrophage function (54) or anti-fibrinolytic activity (55).

Genetic variations in apolipoprotein A5 are other important determinants accounting for differences in response to statins. Plasma TG levels are strongly linked with the rare apoA5 polymorphisms: variants T-1131T > C and C56 > G are associated with elevated triglycerides (56), the rare homozygous forms being linked to extreme TG elevations (57). More recent findings indicate that apoA5 polymorphisms also influence cholesterol homeostasis and may affect the susceptibility to coronary artery disease (58,59). The impact of statin treatment on lipid parameters is not associated with the type or dose of statin and does not significantly differ between carriers and non-carriers of the c.56C > G and c.457G > A polymorphisms (60). In contrast, the LDL-C decrease depends on the presence of the apoA5 C-1131 allele; in fact carriers of this allele respond significantly less to statin treatment compared to the common T-1131T homozygotes (LDL-C $-29.9\% \pm 12.5\%$ versus $-36.6\% \pm 15.1\%$) (60) (Table I).

Statin myopathy: pharmacological bases and genetic factors

Statin-induced myalgia is a frequent phenomenon encountered in daily practice. While reports of severe rhabdomyolysis date back to more than 20 years ago (61), only scattered reports indicated the potential clinical significance of plain myalgia. The emerging clinical trials did not indicate this as a real problem: randomized clinical trials tend to enroll carefully selected patients, and myopathy is often defined based on certain threshold values for plasma CK levels.

The true nature of muscle pain often remains unclear to physicians, as objective biochemical biomarkers are lacking. The vast majority of patients with statin-induced myalgia have normal CK levels, thus a novel sensitive biomarker (also covering these patients) would be greatly appreciated both by patients and physicians. In an earlier report, Phillips et al. (5) identified and investigated a group of 30 patients treated with statins with normal CK and muscle symptoms, who improved after stopping statin therapy for at least 2 weeks. Muscle biopsies showed evidence of mitochondrial dysfunction, including abnormally increased lipid stores, despite normal blood biochemistry. The morphology of de facto muscle changes has also been well described by the group of Draeger et al. (62). They initially reported muscle changes occurring in *all individuals* who had received statins. More recently, gross electron microscopic changes in individuals who had significant muscle pain, in particular those with pain persisting up to several months after statin withdrawal, were described (63).

Very recently Hippisley-Cox et al. (64) have developed four new risk prediction algorithms to quantify the individual absolute risk of an adverse clinical outcome after statin use. The scores were validated using two separate sets of practices from the QResearch (65) and THIN databases (64). The risk of myopathy varies in different ethnic groups, black African and Caribbean groups presenting with the highest risk. Hypothyroidism, type 1 diabetes, chronic liver disease, and treated hypertension were definite risk factors for myopathy in females but not in males. The validation statistics for the algorithms to predict myopathy showed that the risk prediction equation when tested using the THIN database

Table I. Summary of the genetic factors controlling responses to statins.

References	Drug	Polymorphism/mutations	Population/study	Effects/results/conclusions
CYPs				
Kirchheiner et al. 2003 (8)	fluvastatin	CYP2C9*2 (Arg144Cys); CYP2C9*3 (Ile359Leu)	24 healthy non-smoker volunteers	CYP2C9*2 and *3 caused an increased area under the curve for the active fluvastatin enantiomer and reduced the hypocholesterolemic response
Kajinami et al. 2004 (9)	atorvastatin	CYP3A4 (A-290G); CYP3A4 (F189S); CYP3A4 (M445T)	344 hypercholesterolemic patients	The A-290G variant allele was associated with higher levels of post-treatment LDL-C, whereas the M445T variant was associated with lower levels of LDL-C before and after treatment
Willrich et al. 2008 (10)	atorvastatin	CYP3A5*3C (A6986G)	139 hypercholesterolemic patients	CYP3A5*3A is associated with reduced cholesterol-lowering response to atorvastatin in non-African individuals
Zuccaro et al. 2007 (13)	simvastatin fluvastatin	CYP2D6*1/*4; CYP2D6*4/4	100 hypercholesterolemic patients	The CYP2D6*1/*4 and *4/*4 poor metabolizer status is associated with a higher efficacy
ABCB1/ABCG2				
Fiegenbaum et al. 2005 (20)	simvastatin	ABCB1 (1236C>T, 2677G>A/T)	116 hypercholesterolemic patients	Carriers of the ABCB1 1236T variant allele had a greater reduction in total and LDL-C after simvastatin; similar results were observed for the 2677G>A/T polymorphism
Bercovich et al. 2006 (21)	fluvastatin	ABCB1-h4 haplotype (GCCTA)	76 Familial Hypercholesterolemia (FH) patients	ABCB1-h4 causes an increased hypocholesterolemic response to fluvastatin
Tomlinson et al. 2010 (28)	rosuvastatin	ABCG2 (c.421AA versus c.421CC genotypes)	305 Chinese hypercholesterolemic patients	Male carriers of the ABCG2 c.421AA genotype had a significantly larger reduction in LDL-C (−58.4% versus −47.6%) after rosuvastatin
SLCO1B1				
Couvert et al. 2008 (30)	fluvastatin	SLCO1B1*14 allele (c.463C)	724 hypercholesterolemic patients	The *14 allele causes enhanced lipid-lowering efficacy of fluvastatin
Igel et al. 2006 (31)	pravastatin	SLCO1B1(388A>G); SLCO1B1(521T>C); SLCO1B1(-11187G>A)	16 healthy volunteers	There was no significant difference in the lipid-lowering efficacy of pravastatin between the variant haplotype and control groups
Hedman et al. 2006 (32)	pravastatin	SLCO1B1 (521TC/TT)	20 Heterozygous Familial Hypercholesterolemia (HeFH) children and 12 cardiac transplant recipients	Decrease in LDL-C by pravastatin is smaller, and increase in HDL-C is larger in the 521TC carriers as compared with the 521TT carriers
CETP				
Kuivenhoven et al. 1998 (38)	pravastatin	CETP B1/B2 variants	The Regression Growth Evaluation Statin Study Group	Pravastatin therapy slowed the progression of coronary atherosclerosis in B1B1 carriers but not in B2B2 carriers

van Venrooij et al. 2003 (41)	atorvastatin	CETP B1/B2 variants	217 patients with type 2 diabetes	B1B1 carriers have a more atherogenic lipid profile, including low HDL, and they respond better to statin therapy
Winkelmann et al. 2003 (44)	various statins	SNPs1-9 haplotype (TTCAAAGGG); SNPs4-9 haplotype (AAAGGG); SNPs1-6 haplotype (TTCAAA)	98 hypercholesterolemic patients	TTCAAA haplotype is in linkage to the HDL-C rising effect of statins, the TTCAAAGGG and AAAGGG haplotypes associated with triglyceride lowering potency of statins
ApoE				
Ballantyne et al. 2000 (47)	fluvastatin	ApoE three common alleles (ε2, ε3, ε4)	724 hypercholesterolemic patients	Subjects with the ε4 allele had less reduction in LDL-C with fluvastatin, but no difference was recorded in terms of CAD progression
De Knijff et al. 1990 (48)	simvastatin	ApoE three common alleles (ε2, ε3, ε4)	120 FH patients	Female FH patients with the apoE3E3 phenotype responded better to treatment than male FH patients with the apoE3E3 genotype.
Hubacek et al. 2005 (56)	various statins	ApoA5 (c.-1131T > C); apoA5 (c.56C > G); apoA5 (c.4576 > A)	187 adult Caucasians	Carriers of C-1131 allele responded significantly less to statin treatment as compared to the common T-1131 homozygotes (LDL-C $-29.9\% \pm 12.5\%$ versus $-36.6\% \pm 15.1\%$)

explained 42% of the variation in women and 36% in men (64).

Statin myalgia—the basic mechanism(s)

The cellular mechanism(s) of statin-induced muscle adverse events have remained elusive. In this review we wish to cover briefly the recent observations on *chloride channels* and on the *atrogin-1 gene*.

The basic mechanism of statin-induced myalgia may be related to their pharmacological mechanism at the neuronal-muscular end-plate. Statins are powerful antagonists of the chloride (Cl) channels at the muscle membrane level (66). This mechanism may result in complete paralysis after very high statin doses, as noted in the first trials in Japan with very large doses of the early statin monacolin K (67). At doses generally employed today, this muscular effect is elicited to a modest extent. It may, however, impair performance of professional athletes (68), who generally have considerable difficulty in taking statins. Further, and most likely, genetic factors that induce accumulation of statins at the muscle level may result in a modest, sustained contractile response, with consequent myalgia.

A more direct statin-induced muscle toxicity mechanism has been described by Hanai et al. (69). These authors indicated that statins may induce the expression of atrogin-1, a key gene involved in skeletal muscle atrophy. This mechanism is exerted in cultured mouse myotubes as well as in zebra fish embryos (69). Apparently this toxic mechanism may be antagonized by over-expression of PPAR-gamma coactivator-1alpha (PGC-1α) a transcriptional coactivator that induces mitochondrial biogenesis and protects against development of muscle atrophy. This direct cellular toxic mechanism may be additive to the antagonism by statins of muscle differentiation (induced by, e.g., insulin) (70).

Genetic factors underlying statin myotoxicity

The myopathic effect of statins increases with increasing doses of the drug(s) and with factors that increase blood concentrations (71), although plasma drug levels do not adequately predict risk of myopathy (72). Genetic variability in statin liver uptake and statin catabolism have clearly been associated with myopathy. Apparently the major players in this context are the CYP variants and variants affecting influx/efflux systems controlled by OATP1B1 and ABCB1, respectively.

Genetic variants of CYPs

The major CYPs, i.e. CYP3A4, CYP3A5, CYP2D6, and CYP2C9, are all involved in statin metabolism.

Particular interest is in CYP3A4/5, CYP2D6, and CYP2C9, all with functional genetic variants.

As indicated above, the polymorphic CYP2D6 appears to play no role in simvastatin metabolism (16). However, from a collection of clinical cases in the US, Frudakis et al. (73) reported a specific association of atorvastatin and simvastatin-induced myopathy with the CYP2D6*4 variant allele. The frequency of CYP2D6*4 was about 50% for atorvastatin-induced muscle myalgia versus 28% for controls, and a similar gene distribution was found for simvastatin myalgia (49% versus 36%). As well clarified by the PRIMO Study, the expression of broadly defined statin myopathy is heritable (74), and higher doses of statins or of their metabolites are associated with increased risk (75): specifically, the metabolites atorvastatin lactone and p-hydroxyatorvastatin are markedly elevated in patients with atorvastatin myopathy. Thus, it is difficult to exclude fully a possible pharmacokinetic interaction in these patients despite lacking evidence that CYP2D6 would significantly affect statin metabolism. As expected, however, among patients who develop myalgia on atorvastatin a higher percentage of CYP3A5*3 homozygotes was reported; these also displayed higher plasma CK levels as compared with the group of heterozygotes (76).

Genetic variants of SLCO1B1

Statins are transported into the hepatocytes by OATP1B1 (77), encoded by the gene SLCO1B1. Atorvastatin, rosuvastatin (77), simvastatin (78), and pravastatin (79) all share this transport mechanism. Fluvastatin can easily penetrate the hepatocyte membrane because of its lipophilicity or by using other transporters (80).

Polymorphisms in the SLCO1B1 gene have been extensively evaluated. The c.521C polymorphism has a large effect on the pharmacokinetics of the hydrophilic pravastatin (otherwise not metabolized by the CYP450 system) (77). An important gene–gender interaction has been observed for pravastatin kinetics and SLCO1B1. The c.521CC genotype associates with higher plasma pravastatin concentrations, as compared with the c.521TC or c.521TT genotypes in males, but such an association between genotype and plasma concentrations was not observed in females (80). The pravastatin AUC in heterozygous Caucasian carriers of the haplotype *17 (11187G > A, 388A > G, and 521T > C) was 130% ($P = 0.0053$) higher compared to non-carriers; in heterozygous carriers of *15B (388A > G and 521T > C) the mean pravastatin AUC was instead 93% higher ($P = 0.024$) versus non-carriers (81). In a Japanese study a higher frequency of the SLCO1B1*15 allele was described in subjects who presented with myopathy after receiving pravastatin or atorvastatin, and a rare novel mutation (1628T > G) in exon 12 of SLCO1B1 was also reported in a patient who experienced myopathy after pravastatin (82). The c.521CC SNP was finally associated with increased plasma concentrations of atorvastatin and rosuvastatin in white Caucasians (77). All these studies clearly point to the fact that the loss-of-function variants of the SLCO1B1 gene may lead both to reduced liver influx of the drug and probably to a more diffuse tissue distribution of the agent(s), potentially leading to increased muscle uptake and consequent toxicity.

A *genome-wide association study* with 300,000 markers in 85 individuals with definite or initial myopathy and 90 statin-tolerant controls provided further evidence on the role of the SLCO1B1 gene in statin-induced myopathy (83). Myopathy was defined as CK values > 10 times the upper limits of normal (ULN), whereas incipient myopathy was defined as a CK level that was both ≥ 3 times ULN and ≥ 5 times base-line levels, plus an alanine aminotransferase (ALT) level > 1.7 times base-line. All had a history of myocardial infarction and had been taking 80 mg simvastatin daily as part of a trial involving 12,000 participants. A single non-coding SNP, rs4363657, in the SLCO1B1 gene on chromosome 12 (SLCO1B1*5) was in almost complete linkage disequilibrium with a non-synonymous rs4149056 SNP in exon 6. The initial results were further tested in a trial of 40 mg of simvastatin daily involving 20,000 participants (83).

The C allele is common in the general population, with a prevalence of 15%. Individuals who are either heterozygous or homozygous for the C allele make up 14%–22% among European-Americans versus only 1% among African-Americans. The OR for myopathy is in the range of 4.3 (95% CI 2.5–7.2) for carriers of one C allele and 17.4 (95% CI 4.8–62.9) for two C alleles (79). Individuals with the rs4149056 variant (Val174Ala) have an OR for myopathy of 4.5 (95% CI 2.6–7.7) per copy of the C allele and 16.9 (95% CI 4.7–61.1) for two alleles (79). CC homozygotes had an 18% cumulative risk, with myopathy occurring primarily during the first year of treatment, whereas the CT genotype is associated with a cumulative risk of about 3% (79). In contrast, the cumulative risk of myopathy is only 0.6% among TT homozygotes. Overall, more than 60% of the 85 cases in the SEARCH study could be attributed to the rs4149056 C variant (83). This variant most probably reduces the transport activity of OATP1B1 to the liver, with raised plasma concentrations and increased penetration into muscle.

Studies associating the SLCO1B1 polymorphism with the kinetics of simvastatin acid and the risk of

simvastatin-induced myopathy suggest that increased levels of active simvastatin acid is the cause of myopathy (78,83). Confirming this, in a previous report, homozygous participants with the SLCO1B1 c.521T > C SNP had a significantly increased mean AUC of active simvastatin acid (3.2-fold), atorvastatin (2.4-fold), and rosuvastatin (1.7-fold) compared with the c.521TT genotype, whereas no effect was seen for fluvastatin and simvastatin lactone (77,78,80). A more extensive overview of the transport system heterogeneity was reported in the STRENGTH study, involving 509 patients randomized to either atorvastatin 10 mg, simvastatin 20 mg, or pravastatin 10 mg for 8 weeks, followed by an additional 8 weeks of treatment with 80 mg, 80 mg, or 40 mg of these statins, respectively (84). The SLCO1B1*5 allele was significantly more frequent among the 71 subjects who developed myalgia and/or discontinued treatment due to musculoskeletal side-effects. Moreover, the authors reported that carriers of the SLCO1B1*5 allele were at a 2-fold relative risk of mild statin-induced side-effects, the majority of whom with normal CK levels (84).

Genetic variants of ABCB1 and ABCG2

Efflux systems have been studied less extensively. In the case of ABCB1 it has been reported that the AUC of simvastatin acid and atorvastatin was increased approximately 60% in homozygous individuals for the c.1236T-c.2677T-c.3435T haplotype versus homozygotes for the reference c.1236C-c.2677G-c.3435C haplotype; no effect was seen on lactones (85). This study as well as the previously quoted report by Keskitalo et al. (27) evaluating the effects of ABCG2 polymorphisms on atorvastatin AUCs failed, however, to show any clear correlation between AUC changes and muscular side-effects.

All of these studies thus confirm that there may be a strong genetic susceptibility to both myopathy and statin-induced myalgia in the absence of elevated CK values. Therefore, genetic testing may provide important prognostic information.

Major histocompatibility complex and other genes affecting muscular side-effects

The expression of the major histocompatibility complex class I (MHC-I) was studied in eight patients with progressive symptoms maintained after cessation of statin therapy (86). All of them had myofiber necrosis, and three had evidence of inflammatory infiltrates. In seven cases, patients responded to immunosuppressive therapy, and one improved spontaneously. MHC-I staining was up-regulated in non-necrotic fibers in all, whereas MHC-II was negative in all. The authors hypothesized that myopathy may have been initiated by statin-induced endoplasmic reticulum stress response, maintained after therapy by the up-regulation of MHC-I. The over-expression of MHC-I could represent another mechanism by which statins damage muscle, and the gene could conceivably carry polymorphisms that modulate this effect (86).

Finally, *vascular homeostasis genes* may have an impact on myalgia. In 102 patients, 19 SNPs were selected from ten candidate genes involved in vascular homeostasis. A significant association was found between SNPs in both the angiotensin II type 1 receptor and nitric oxide synthase 3 with an increase in CK levels during statin therapy (87). These results suggest that vascular smooth muscle function may play a role in the muscular side-effects of statins (Table II).

Summary and conclusions

The current growing interest in pharmacogenetics is addressed both to an improved understanding of activity/adverse effects of currently available drugs and also, possibly, to providing a guideline for new molecules to be developed. It can definitely offer important information to any drug user. The wide availability of highly sophisticated technologies for detecting, e.g., SNPs associated with differences in drug responses or increased incidence of side-effects, have made pharmacogenetic data possibly accessible to any physician (88). On the other hand, it is common knowledge that very few physicians make direct use of these technologies and, further, that most physicians have a very vague understanding of what these may offer.

An objective evaluation of the case of statins indicates that, as yet, pharmacogenetics is not offering a critical amount of information to drug prescribers or users. In terms of hypocholesterolemic activity, it is evident that, aside from the case of extreme non-responders (e.g. with complete CYP7A1 deficiency) (25), the most widely studied phenotypes indicate differences in drug responses that generally go unnoticed by the practicing physician and that, frequently, may just be handled by raising drug doses. There is, indeed, the potential that some haplotype data could provide more useful information, but this will need improved education. The interest in pleiotropic effects of statins, i.e. anti-inflammatory, pro- or anti-apoptotic, anti-oxidant, vasodilatory, etc., has certainly grown to very high levels (1). It has not, however, provided convincing data on a direct correlation with the cardiovascular preventive activity.

Adverse effects are probably the most clinically significant problem, in view of the increasing number

Table II. Summary of the basic mechanisms and genetic factors underlying statin myopathy.

References	Drug	Polymorphism/ mutations/biopsies	Population/study	Effects/results/conclusions
Basic mechanism(s)				
Philips et al. 2002 (5)	various statins	muscle biopsy	30 patients with normal CK	Patients reported muscle symptoms. Muscle biopsies showed mitochondrial dysfunction, including abnormally increased lipid stores
Draeger et al. 2006 (62)	various statins	muscle biopsy	22 patients	Patients had skeletal muscle damage including break-down of the T-tubular system and subsarcolemmal rupture
Mohaupt et al. 2009 (63)	various statins	muscle biopsy	83 patients	Patients with muscular pain, in particular those with muscular side-effects persisting several months after statin withdrawal
Pierno et al. 2006 (66)	various statins	muscle	male Wistar rats	Statins are antagonists of the Cl channels at the muscle membrane level. This mechanism may result in complete paralysis in rats after very high doses of statins, inducing myalgia
Hanai et al. 2007 (69)	lovastatin	muscle biopsy	humans with statin myopathy; mice myotubes and zebra fish embryos	Lovastatin may induce the expression of atrogin-1, a key gene involved in skeletal muscle atrophy
CYPs				
Frudakis et al. 2007 (73)	atorvastatin/simvastatin	CYP2D6*4	case control study	CYP2D6 polymorphism may be associated with statin-induced myopathy
Wilke et al. 2005 (76)	atorvastatin	CYP3A5*3 homozygosis	case control study (137 patients)	Carriers developed myalgia and had higher plasma CK levels versus heterozygotes
ABCB1/ABCG2				
Keskitalo et al. 2008 (85)	atorvastatin/simvastatin	ABCB1 haplotypes (c.1236T-c.2677T-c.3435T-c.1236C-c.2677G and c.3435C)	24 healthy Finnish volunteers	Homozygote carriers of the c.1236T-c.2677T-c.343T haplotype showed increases in the AUC of simvastatin acid and atorvastatin, both approximately 60%
Keskitalo et al. 2009 (27)	atorvastatin, rosuvastatin	ABCG2 (c.421AA and c.421CC genotypes)	32 healthy Finnish volunteers	The AUC of atorvastatin about 70% higher and that of rosuvastatin 144% higher in carriers of the ABCG2 c.421AA genotype
SLCO1B1				
Morimoto et al. 2004 (82)	pravastatin/atorvastatin	SLCO1B1*15 allele rare novel mutation (1628T > G)	Japanese study	All subjects presented with myopathy. In one patient with this rare novel mutation in exon 12 of SLCO1B1 it resulted in myopathy after pravastatin
Link et al. 2008 (83)	simvastatin 80 mg	rs4149056 C variant (Val174Ala)	SEARCH study (85 cases/90 controls)	This variant has an OR for myopathy of 4.5 per copy of the C allele and 16.9% for two alleles. CC homozygotes have an 18% cumulative risk of myopathy during the first year of treatment
Voora et al. 2009 (84)	atorvastatin/simvastatin/ pravastatin	SLCO1B1*5 allele	STRENGTH study (509 patients)	Carriers were at a 2-fold relative risk of mild statin-induced side-effects despite normal CK levels
MHC-I				
Needham et al. 2007 (86)	various statins	muscle biopsy	8 patients with myopathy	The mechanism of myopathy may involve an endoplasmic reticulum stress response with associated up-regulation of MHC-I expression and antigen presentation by muscle fibers
Vascular homeostasis genes				
Ruano et al. 2005 (87)	various statins	19 SNPs	102 patients	SNPs in the angiotensin II type 1 receptor and nitric oxide synthase 3 genes were significantly associated with CK activity

of patients complaining of muscle pain, in some cases even leading to lawsuits against the drug producer (89). Muscle tolerability of statins is, as generally known, not ideal. Most professional athletes cannot tolerate statins when exposed to significant muscle efforts (64). On the other hand, in conditions where drug distribution to muscle is increased, e.g. due to changes in the SLCO1B1 gene, the risk of muscular side-effects may rise (83,84). Evaluating SLCO1B1 polymorphisms in an effort to find the critical variants could prevent muscle pain/damage in individuals potentially at high risk (liver or renal patients, or with pre-existing muscular diseases). Recently, Niemi (90) recommended evaluation of the SLCO1B1 polymorphism, specifically the presence of the c.521T > C SNP, clearly associated with an enhanced myopathy risk, particularly in patients on high statin dosages. He also recommended evaluation of the ABCG2 polymorphism, for which, however, no data are currently available in the context of statin therapy: the association with rosuvastatin efficacy may suggest a more extensive evaluation of ABCG2 polymorphism with this newer statin, now of wide-spread clinical use.

Gene polymorphisms leading to better or worse efficacy of statins seem, instead, not always to be associated with clear changes in event reduction. Indeed, in some cases, e.g. the ABCB1 polymorphisms, gene variants associated with greater reductions in total/LDL-cholesterol proved not to be associated with a higher reduction of MI risk; in the case of ABCG2, a complex relation with the urate excretory mechanisms makes evaluation of the associated risk quite complex (26). It seems that a systematic genetic screening for some known SNPs would most likely improve the muscle safety of the statin treatment but would not necessarily improve cardiovascular disease risk reduction.

Declaration of interest: The authors report no conflicts of interest.

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