Atherosclerosis 240 (2015) 260–271

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Genetic and immunologic susceptibility to statin-related myopathy

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ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form
13 March 2015
Accepted 17 March 2015
Available online 21 March 2015

Keywords:
SLCO1B1
Anti-HMGCR
Statin-related myopathy
Pharmacogenomics

ABSTRACT

Statin-related myopathy (SRM) undermines drug adherence that is critical for achieving the benefits of lipid-lowering therapy. While the exact mechanism of SRM remains largely unknown, recent evidence supports specific genetic and immunologic influence on the development of intolerance. Genes of interest include those involved in the pharmacokinetics of statin response (i.e. drug metabolism, uptake transporters, and efflux transporters), pharmacodynamics (i.e. drug toxicity and immune-mediated myopathy), and gene expression. We examine the influence of genetic and immunologic variation on the pharmacokinetics, pharmacodynamics, and gene expression of SRM.

1. Introduction

The pharmaceutical drug class 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are one of the most effective therapies to manage atherosclerosis in the prevention of primary and secondary cardiovascular disease [1]. Despite their potent ability to treat hypercholesterolemia, statin adherence and effectiveness can be undermined by adverse muscle effects [2]. Although no consensus guidelines exist for the definition of statin-related myopathy (SRM) [3–5], terminology recommendations from The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute are the most widely adapted [5]. Myopathy occurs in several different forms, and the definition serves a general purpose to describe any disease of the muscle [5].

Generally well tolerated, the true incidence of SRM is relatively uncertain, ranging from 1.5% to 5% in randomized controlled trials (comparable to placebo groups) [6], compared to 5–20% in observational studies [7–9]. In addition, muscle symptom complaints in a double-blinded, randomized study of statin naïve patients suggests a doubling of incidence from 4.6% to 9.4% when treated with high dose atorvastatin therapy [10]. Nonetheless, individuals with a history of statin intolerance were excluded in prior statin outcome trials, which would tend to favor greater similarity in rates of myopathy between the statin and placebo groups.

Genomic research has identified specific genetic variants involved in the metabolism of statins and consequential muscle toxicity. The focus of this review is to present the genes most adequately characterized with the pharmacokinetics, pharmacodynamics, and gene expression of SRM.

2. Methods

A computerized literature search was performed through PubMed databases to identify English-language, full-text articles in peer-reviewed journals, published from January 1, 1980, through April 1, 2014, with the purpose to examine genetic factors associated with SRM. Inclusion criteria for SRM studies were 1) a form of muscle toxicity (myalgia, myopathy, or rhabdomyolysis) and 2) to have available genotype information. All types of study designs (including cohort, case–control, and prospectively randomized trials) were included. The keywords utilized for the search in all text fields were “statin and myopathy” alone or in combination

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.025
0021-9150/

with “myalgia”, “muscle,” “myotoxicity,” “myositis,” “rhabdomyolysis,” “simvastatin,” “SLCO1B1”, “cytochrome p450,” “pharmacogenomics,” “pharmacokinetics,” “GWAS,” and “genetics.”

A separate, similar search to identify articles related to immune mediated necrotizing myopathy (IMNM) was established. Inclusion criteria for these studies were 1) muscle symptom persistence despite statin cessation and 2) have available immunologic information. We used the Bohan and Peter diagnostic criteria [11,12] to exclude studies reporting on the alternative inflammatory myopathies, polymositis and dermatomyositis. All study designs were included. Again, a computerized literature search was performed as above using the key words “statin and myopathy” alone or in combination with “HMG-CoA reductase inhibitors,” “anti-HMGCR antibody,” “autoimmune myopathy,” “immune-mediated necrotizing myopathy,” “necrotizing myopathy,” “toxic myopathy,” “inflammatory myopathy,” and “immunogenomics.”

For both search models, we further identified articles not found during the initial electronic search that would be useful for this review through reference lists from these articles and our personal records, respectively.

3. Genetic markers of statin myopathy

Recent data suggest a specific genetic influence on the development of intolerance, at least for some statins. Broadly, these risk factors have been classified into subcategories relating to statin pharmacokinetics, pharmacodynamics, and gene expression.

3.1. Genetic variation in statin pharmacokinetics

The myopathic effect of statins is related to higher doses of the drug and with factors that increase blood concentration, although risk prediction of myopathy cannot be entirely predicted by plasma drug levels [13,14]. Some *in vitro* and clinical data suggest the importance of genetic variation with respect to statin metabolism [15]. Variations in genes such as those that impact statin first pass pharmacokinetics (e.g. p450 gene family), increase systemic exposure of statins (e.g. ABCB1 and ABCG2) [16–21], or involve modification of an organic anion transporting polypeptide (e.g. SLCO1B1) have been documented in Table 1.

3.1.1. Statin uptake transporters

Genetic variation of the SLCO1B1 gene has been extensively documented, and two common polymorphisms have been associated with OATP1B1, altering statin pharmacokinetics: the rs4149056 (Val174Ala/SLCO1B1*5) and rs2306283 (Asp130Asn) alleles [22]. The encoded OATP1B1 transporter facilitates movement of hydrophilic statins into hepatocytes [23–25]. The role of the SLCO1B1*5 polymorphism in SRM is summarized in Table 1 [22,26–32].

In the GWAS substudy of The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, SLCO1B1 rs4363657 showed strong linkage disequilibrium with the non-synonymous rs4149056 SNP, in patients taking simvastatin 80 mg/d [26]. SLCO1B1*5 showed a significant association with clinical myopathy ($p = 4 \times 10^{-9}$). This finding was replicated in the Heart Protection Study sample with a dose of 40 mg/d simvastatin [33], while additional studies have validated an independent association between the SLCO1B1*5 allele and myopathy risk [22,26–29,33,34]. The odds ratio for myopathy was 4.5 (95% CI 2.6–7.7) per copy of the SLCO1B1*5 allele, and 16.9 (95% CI 4.7–61.1) in homozygotes carriers compared with homozygotes non-carriers. An increased risk of adverse effects with additional copies of the SLCO1B1*5 risk allele has been supported by other studies [30,34]. Of note, risk of myopathy was greatest in the first year of statin therapy, particularly for homozygote carriers (15%) compared to heterozygotes (1.3%) and homozygote non-carriers (0.3%).

The Statin Response Examined by Genetic HAP Markers (STRENGTH) trial validated female sex to be independently associated with adverse events (OR, 95% CI, p-value): 2.2 (1.4–3.6), $p = 0.001$ [34]. In a study of patients with diabetes prior to initiating statin therapy (simvastatin was the most commonly prescribed therapy), a statin dose response effect for the development of myopathy was noted [22].

Myopathy associated with the SLCO1B1*5 allele may be statin specific [27–32]. In patients receiving simvastatin, there was a 3-fold increase in the risk of myopathy (one-tailed p-value = 0.042), whereas in atorvastatin users no increased risk of myopathy was noted (OR, 95% CI, p-value): 1.06 (0.22–4.80), $p = 0.48$ [27]. Other studies assessing drug-specific findings have suggested similar results [30,31,35]. This outcome has also been noted in rosuvastatin treated patients from the JUPITER trial [32].

Genetic sub-studies of large statin clinical trials have revealed that SLCO1B1*5 alters pharmacokinetics of statins, with subsequent changes lipid-lowering efficacy. For example, per allele, LDL-C was lowered by 1.15% in a simvastatin study [36] and 2.6% with rosuvastatin [37], while the presence of the rs4149056 SNP was associated with less LDL cholesterol lowering response to pravastatin 40 mg: 32% in homozygote carriers vs. 36% in heterozygotes [38]. The effect on lipid lowering appears small, and it remains unclear if there is an association with cardiovascular outcomes [39]. Furthermore, in the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS), the *5 allele was associated with improved high-density lipoprotein cholesterol in response to atorvastatin [40].

Despite robust evidence suggesting that carriers of the SLCO1B1*5 allele are at increased risk of myopathy, the predictive value and clinical utility of this marker has yet to be fully defined for all statins. Nonetheless, safety guidelines on the initiation of high dose simvastatin have been issued by the FDA [41]. Further, The Pharmacogenomics Resource for Enhanced Decisions in Clinical Care and Treatment (PREDICT) algorithm suggests making simvastatin dose adjustments or choosing an alternative within the same drug class according to SLCO1B1 status [42]. Congruent arguments state that the statin dose for carriers of the SLCO1B1*5 allele should be lowered, and lowered further in homozygote carriers [16]. SLCO1B1 gene information may be influential in predicting potential side effects and statin dosing strength as a means of individualizing treatment [43], however at this time is not recommended by expert consensus panels [44].

3.1.2. Drug metabolism

The CYP statin metabolic pathway appears most important in the setting of concurrent medication use [45] that utilizes the same CYP isoenzyme [46]. CYP3A4/5, CYP2D6, and CYP2C9 have genetic polymorphisms that can lead to activity ranging from complete deficiency to ultrafast metabolism causing elevated drug levels and potential toxicity [47–50], while decreased or absent activity has been associated with a lack of therapeutic activity [51]. With the exception of pravastatin, all statins undergo metabolism by CYP isoenzyme systems [52]. CYP3A4 system is responsible for the metabolism of lovastatin, simvastatin, and atorvastatin [52]. Inhibition of this system has been shown to elevate serum statin concentration, increasing the risk of serious muscle complications [53]. Nearly half of all drugs currently available are biotransformed in the liver primarily by the CYP3A4 system [54], and fortunately CYP3A4 has few polymorphisms that can affect drug function [55], not being associated with SRM [56].

CYP2D6 is an important isoenzyme, metabolizing 24–30% of all