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Review

Statin myotoxicity: A review of genetic susceptibility factors

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Abstract

The 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) are among the most common medications prescribed worldwide, but their efficacy and toxicity vary between individuals. One of the major factors contributing to intolerance and non-compliance are the muscle side-effects, which range from mild myalgia through to severe life-threatening rhabdomyolysis. One way to address this is pharmacogenomic screening, which aims to individualize therapy to maximize efficacy whilst avoiding toxicity. Genes encoding proteins involved in the metabolism of statins as well as genes known to cause inherited muscle disorders have been investigated. To-date only polymorphisms in the *SLCO1B1* gene, which encodes the protein responsible for hepatic uptake of statins, and the *COQ2* gene, important in the synthesis of coenzyme Q10, have been validated as being strongly associated with statin-induced myopathy. The aim of this review is to summarize studies investigating genetic factors predisposing to statin myopathy and myalgia, as the first step towards pharmacogenomic screening to identify at risk individuals.

Keywords: 3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors; Statins; Pharmacogenomics; Genetics; Myopathy; Myalgia; Muscle

1. Introduction

The 3-Hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) are the most potent drugs available to treat hypercholesterolaemia, which is implicated in the pathogenesis of coronary artery disease, cerebrovascular disease and peripheral vascular disease. Statins are among the most widely prescribed drugs in the USA [1], and are used by an estimated 38 million people in the USA [2]. However, their effectiveness has been undermined by their adverse effects, particularly on skeletal muscle. This was highlighted with the withdrawal of Cerivastatin in 2001 because of an increased frequency of severe rhabdomyolysis and death. Adverse muscle reactions are one of the most common reasons for non-compliance with statin therapy [3,4], and they can have a significant impact on quality of life [5]. The myotoxicity of statins can be mild such as asymptomatic hyperCKaemia [6], and increasing in severity through a spectrum of myalgia without hyperCKaemia, proximal weakness with hyperCKaemia, necrotizing autoimmune myositis (NAM), to severe and at times fatal rhabdomyolysis.

The true incidence of statin myopathy is still uncertain, and is dependent on various factors including the definition used for statin myopathy, the dose and type of statin, presence of other co-medications [7] and levels of physical exercise [8]. Whilst clinical trial data suggested the incidence of muscle symptoms was similar to placebo [9–11], some subsequent large community-based studies have found an incidence of mild muscle symptoms as high as 10–20% [12–14]. However most studies have agreed that the risk of severe muscle effects such as rhabdomyolysis is very low (0.003–0.1%) [7,12,15–19]. One of the major problems in interpreting and comparing

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the results of large observational community-based studies has been the lack of strict definitions of statin myopathy, and the fact that many studies have relied on patient self-reporting of muscle side-effects without objective assessment by experienced neuromuscular specialists.

The risk factors for developing statin myopathy are multiple and include age, exogenous influences, nutritional status, co-morbidities and other concomitant medications, (Table 1) [15,20–22]). Increasingly, genetic variations are being recognized to play a role in determining both an individual's therapeutic response and propensity for toxicity to statins, and this is the basis for the present review Recent progress in this field has been preceded by technological advances allowing rapid gene sequencing and the development of single nucleotide polymorphism (SNP) and copy number variation (CNV) databases to help interpret this information.

The aim of this review is to summarize studies investigating genetic factors predisposing to statin myopathy and myalgia, as the first step towards pharmacogenomic screening to identify at risk individuals. In order to do so, all studies investigating statin myopathy or myalgia were reviewed, and these terms are defined as muscle weakness or pain, with or without elevated creatine kinase, (CK). As a background to considering pharmacogenomic studies of relevance to statin myopathies, the underlying pathophysiological effects of statins on muscle will first be reviewed briefly, (Section 2), followed by a review of the pharmacogenomics studies published to-date, (Section 3). Addressing clinical treatment questions is beyond the scope of this review, and has been extensively reviewed previously [15].

2. Pathophysiological mechanisms

A number of different mechanisms have been proposed for the myotoxic effects of statins and the development of myopathy, (Fig. 1), and there is still uncertainty as to their relative importance, (reviewed in [15]). It is likely that certain mechanisms are more important in some individuals than others, and these differences may reflect underlying genetic variations and susceptibilities which warrant investigation.

One of the most important proposed mechanisms is reduced synthesis of the isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, resulting in reduced prenylation of small GTPase proteins involved in cell growth and maintenance [23–27]. It is known that GTP-binding protein signaling pathways are activated by exercise, particularly the mitogen-activated protein (MAP) kinases, which are important in maintaining skeletal muscle homeostasis during exercise-induced stress [28,29]. Inhibition of this pathway could also help explain the increased CK levels in statin-treated athletes [8,30,31].

Another consequence of reduced farnesyl-pyrophosphate synthesis is impaired production of ubiquinone (Coenzyme Q_{10}) [32–35], which may lead to mitochondrial dysfunction and reduced energy production [36]. Biopsies from statin-treated patients can have increased numbers of COX-negative and ragged-red fibres [37–39]. However these changes are mainly seen in older adults (>60 years), suggesting that there may be an added effect of aging. In addition, Coenzyme Q_{10} supplementation may ameliorate statin-induced myopathy although this has not been confirmed in all studies [40–42]. It is possible that individuals with mtDNA

Table 1
Risk factors for developing statin-induced myopathy or myalgias.

Advanced age, frailty	(Especially >80 years) [21]
Patient factors	
Female gender	[94]
Co-morbidities	Untreated hypothyroidism [13,135,136]
	Low Vitamin D levels [137]
	Chronic renal insufficiency especially when associated with diabetes [21]
Physical exercise	[8,31,108]
Surgery	The American Heart Association recommends temporary cessation of statins prior to major surgery [21]
History of statin myopathy	Personal or family history of statin myopathy [13]
Drug factors	
Higher statin dose	[7,138]
Type of statin	Higher risk with lovastatin, simvastatin and atorvastatin, lower with pravastatin and fluvastatin [13,16]
Interacting drugs	CYP2C9 enzyme inhibitors such as warfarin may affect fluvastatin and rosuvastatin levels
	CYP3A4 enzyme inhibitors such as diltiazem, erythromycin, fluconazole, and protease inhibitors [139–141] as well as grapefruit juice (>200 mls daily), increase levels of simvastatin, atorvastatin and lovastatin increasing the risk of muscle toxicity
	Gemfibrozil, increases plasma concentrations of simvastatin, pravastatin, lovastatin and rosuvastatin. [142–145]
	Amiodarone increases risk of simvastatin toxicity (relative risk of nearly 10) [97,146]
	Alcohol abuse

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