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Myotoxicity of statins: Mechanism of action

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ABSTRACT

Statins are effective drugs to reduce cardiovascular events secondary to dyslipidemia; however, they cause frequent undesirable side effects. The incidence of statin-induced myotoxicity (SIM) is presented by 7 to 29% of patients, depending upon the report. SIM may develop in presence of abnormally high concentrations of statins in the myocyte and/or in presence of muscular conditions that may predispose to SIM. High concentrations of statins in the myocyte may occur whenever the activity of liver influx membrane transporters, namely OATP1B1, of drug metabolizing enzymes, and of liver and muscular efflux transporters, MDR1 and BCRP, is reduced. In the muscle, conditions that may predispose to SIM include mitochondrial damage with disruption of the mitochondrial respiratory chain and decreased production of ATP, increase of ROS, and leak of cytochrome c and Ca^{2+}. In the sarcoplasma, statins activate MAPK and diminish the RhoA/AKT/mTOR/PGC-1α pathway. All these effects contribute to activate apoptosis, proteolysis, and muscle remodeling. Moreover, in the sarcoplasma, statins can reduce the resting chloride channel conductance, as well as lactate efflux. These changes will be responsible of fatigue, cramps, myalgia and elevation of serum CK. To date, besides avoiding drug-drug interactions and alcohol consumption, and correcting hypothyroidism, two strategies could be useful to prevent/diminish SIM, e.g. gradual dose titration with statins less prone to produce SIM, and high supplements of vitamin D in subjects with low plasma concentrations of 25(OH) D_3.

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Abbreviations: AKT, protein kinase B; AMPK, AMP-activated protein kinase; Bax, Bcl-2-associated X; Bcl-2, B-cell lymphoma 2; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CaMKII, calmodulin kinase II; CaMKK, Ca^{2+}/calmodulin-dependent kinase kinase; CAT, catalase; CK, creatine kinase; ClC-1, chloride channel; CREB, response element-binding protein; DCA, dichloroacetate; FoxO3, forkhead box O3; FPP, farnesyl pyrophosphate; gCl, resting chloride channel conductance; GGPP, geranylgeranyl pyrophosphate; GLUT4, glucose transporter 4; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HMG-CoAR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IGF-1, insulin-like growth factor-1; Insig, insulin-induced gene; LDL-C, low density lipoprotein-cholesterol; LKB1, liver kinase B1; MAFbx or atrogin-1, muscle atrophy F-box; MCT, monocarboxylate transporter; MDR1 or P-glycoprotein, multidrug resistance 1; MEF2, myosin enhance factor 2; mPTP, mitochondrial permeability transition pore; MRP2, multidrug resistance protein 2; mTOR, mammalian target of rapamycin; MuRF-1, muscle RING-finger protein-1; NADH, reduced β-nicotinamide adenine dinucleotide; NTCP, sodium-dependent taurocholate cotransporting polypeptide; $O_2^{\cdot-}$, superoxide; OATP, organic anion transporting polypeptide; OR, odds ratio; p38MAPK, p38 mitogen-activated protein kinase; PCSK9, proprotein convertase subtilisin–kexin type 9; PDC, pyruvate dehydrogenase complex; PDK, piruvate dehydrogenase kinases; PGC, transcription factors peroxisome-proliferator-activated receptor coactivator; PPARγ, peroxisome-proliferator activating receptor γ; RhoA, Ras homolog gene family member A; ROS, reactive oxygen species; RYR3, ryanodine receptor 3; SERCA3, sarco-endoplasmic reticulum transporting Ca^{2+} ATPase 3; SIM, statin-induced myotoxicity; SIRT5, sirtuin 5; SLC, solute carrier transporters; SNP, single nucleotide polymorphism; SOD, superoxide dismutase; SR, sarcoplasmic reticulum; TCA, tricarboxylic acid.

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1. Introduction

The most effective oral agents for the prevention and treatment of cardiovascular diseases associated to dyslipidemia are the statins. Lovastatin and simvastatin are administered in the inactive lactone form, and pravastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin in the active β-hydroxy acid form. Statins are reversible competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoAR), and as such reduce intracellular synthesis of cholesterol. The pharmacological response of statins depends upon their ability to reach the hepatocyte where they will inhibit HMG-CoAR (Schachter, 2005). Inhibition of HMG-CoAR will not only diminish the synthesis of cholesterol, but also that of ubiquinone, steroids, bile acids, vitamin D, as well as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) (Fig. 1) (Brown, Ikonen, & Olkkonen, 2014). Statins elicit pleiotropic effects on the cardiovascular system, effects in part secondary to the Thr^{172} phosphorylation of AMP-activated protein kinase (AMPK) (Sun et al., 2006).

Approximately 25% of the world population older than 65 years take a statin for primary or secondary prevention of cardiovascular diseases (Gu, Paulose-Ram, Burt, & Kit, 2014; Wallach-Kildemoes, Stovring, Holme Hansen, Howse, & Pétursson, 2016). Although statins are generally well tolerated, patients treated with statins may complain of diminished lower extremity muscular strength (Loenneke & Loprinzi, 2016). Moreover, statins may produce statin-induced myotoxicity (SIM), including heterogeneous clinical manifestations such as muscle weakness, muscle pain or aching (myalgia), stiffness, muscle tenderness, cramps, and arthralgia. Any of these symptoms can be presented with or without an elevation of creatine kinase (CK) serum concentrations. On the contrary, elevation of serum CK might be the only sign of SIM.

The prevalence of SIM is subject of considerable discussion because the clinical reports vary widely, due to the lack of uniformity to define SIM, and because large randomized trials do not report reliable estimates of statin intolerance and furthermore, may not reflect clinical practice (Guyton et al., 2014; Muntean et al., 2017). In clinical practice, the incidence of SIM range from 7 to 29% of patients treated with statins (Cohen, Brinton, Ito, & Jacobson, 2012; Zhang et al., 2013). Recently, an international expert workshop on SIM proposed a standardization of the terminology and of the phenotypes (Alfirevic et al., 2014). Table 1 summarizes the classification of the different phenotypes of SIM. Asymptomatic elevation of serum creatine kinase (CK) (SIM 0) and mild myalgia (SIM 1) are not always associated to statins, they may be secondary to other drugs, diseases or simply to exercise. However, SIM 0 and/or SIM 1 are reported by around 30% of patients taking statins; in patients with SIM 0 and SIM 1, statins are usually not discontinued. In patients with SIM 2, the myalgia is sufficiently important to reduce patient's quality of life, in which case, statins are discontinued. More severe forms of SIM (3-5) are accompanied by various degrees of muscle necrosis, and statins are always discontinued. For SIM 2-5, the discontinuation of the statin will relieve the symptoms. The statin-induced autoimmune myopathy (SIM 6) is caused by autoantibodies against HMG-CoAR, the pharmacological target of statins; after statin discontinuation, symptoms usually persist (Stroes et al., 2015).

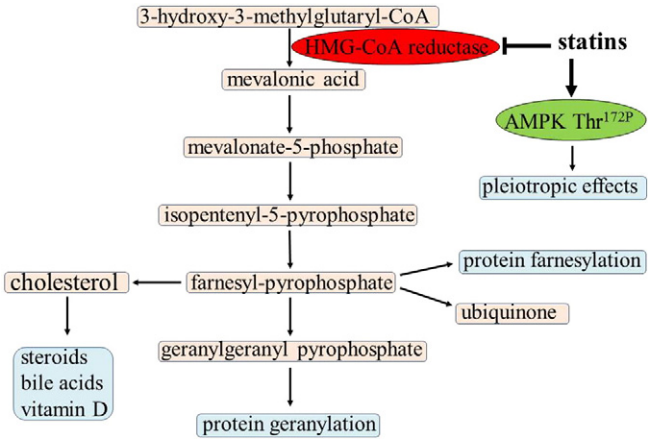

Fig. 1. Schematic representation of the mevalonate pathway

Table 1
Statin-induced myotoxicity (SIM) classification and prevalence.
Adapted from Alfirevic et al., 2014.

Classification	Phenotype	Prevalence
SIM 0	CK elevated <4 × ULN No myalgia	1.5–26%
SIM 1	CK not elevated Mild myalgia	0.3–33%
SIM 2	CK elevated <4 × ULN Severe myalgia	0.02–0.2%
SIM 3	CK >4 × ULN<10 × ULN Myopathy	5/100,000 patients-year
SIM 4	CK >10 × ULN<50 × ULN Severe myopathy	0.11%
SIM 5	CK >10 × ULN Rhabdomyolysis	0.1–8.4/100,000 patients-year
SIM 6	HMG-CoAR antibodies Autoimmune-mediated necrotizing myositis	~2/1,000,000 patients-year

CK creatine kinase; ULN upper limit of normal; HMG-CoAR 3-hydroxy-3-methylglutaryl-CoA reductase.

There is some evidence supporting that in patients with SIM, plasma concentrations of statins and/or its metabolites are elevated, suggesting that pharmacokinetic mechanisms underlie SIM. Effectively, Hermann et al. (2006) reported that in patients with atorvastatin-induced SIM, plasma concentrations of *o*-hydroxyatorvastatin, *p*-hydroxyatorvastatin, atorvastatin lactone and p-hydroxyatorvastatin lactone were significantly higher than the plasma concentrations of these compounds estimated in patients without SIM. However, this is not always the case, since SIM has been reported in presence of plasma concentrations of statins in between the accepted normal range (Phillips et al., 2002). Therefore, at least two conditions must underlie SIM mechanism of action: pharmacokinetic conditions leading to statin accumulation into the muscle, and myocyte conditions favouring statin toxicity. Indeed, numerous risk factors, such as age, gender, ethnicity, frailty, genetics, presence of other diseases, and polypharmacy (Mancini et al., 2016; Stroes et al., 2015) will contribute to one or the other group of conditions. This review will first discuss the pharmacokinetic conditions that may increase statin concentrations into the myocyte, and thereafter, present the conditions in the muscle that may trigger SIM.

2. Pharmacokinetic conditions resulting in statin accumulation in the myocyte

2.1. Hepatic handling of statins

Once absorbed, statins (acid and lactone forms) have to reach the liver to elicit the desired effect, e.g. inhibit HMG-CoAR, and be eliminated by biotransformation. Statins will pass through the fenestrations of the endothelial cells, attain the space of Disse, and ultimately the hepatocytes (Fig. 2). Being organic acids, the passage of statins into the hepatocyte is mediated by membrane carriers of the solute carrier transporter (SLC) superfamily, primarily by members of the organic anion transporting polypeptide (OATP). In the hepatocyte (Fig. 3), the major influx transporters of statins are OATP1B1 (encoded by *SLCO1B1* and expressed primarily in the liver and small intestine) and OATP1B3 (encoded by *SLCO1B3*). Less importantly, OATP2B1 (encoded by *SLCO2B1*) may also contribute to the influx transport of statins (see review Bosgra et al., 2014; Kunze, Huwyler, Camenisch, & Poller, 2014; Rodrigues, 2010). Other influx transporters of statins include OATP1A2

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