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International Journal of Clinical Anesthesiology

Editorial

Statin-Induced Myopathy, RYR1 Gene Sequence Variations and Association with Malignant Hyperthermia Susceptibility

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Submitted: 19 July 2017
Accepted: 19 July 2017
Published: 21 July 2017
ISSN: 2333-6641

EDITORIAL

Statins (3-hydroxy-3-methylglutaryl coenzyme-A or HMG Co-A reductase inhibitors) are a very established class of drugs for the treatment of hypercholesterolemia. However, 10%-15% of patients report statin-induced miopathy (SIM) [1]; myotoxicity is dose-dependent and resolves after discontinuation of therapy. SIM has a highly variable clinical presentation including muscle fatigability, moderate or strong myalgia with normal or increased creatine kinase (CK) activity, and rarely rhabdomyolysis. Several mechanisms have been proposed to explain SIM, e.g., reduced synthesis of mevalonate and consequently of production of isoprenoids such as coenzyme Q10 and prenylated proteins, reduced function in drug metabolizing or transporting enzymes, and alteration of calcium homeostasis in muscle cells. Genetic factors can predispose to develop SIM. Sequence variants (SVs) in the *CoQ2* gene encoding the enzyme polyprenyltransferase involved in the synthesis of coenzyme Q10, in genes encoding the cytochrome P450 enzymes superfamily (*CYP2D6* (coumarin 7 hydroxylase), *CYP3A4* (glucocorticoid inducible p450) and *MDR-1* (multidrug resistance 1, ABCB1 transporter) genes), and in the *SLCO1B1* gene encoding a membrane-bound sodium-independent organic anion transporter protein (OATP1B1), involved in active cellular influx of many endogenous and xenobiotic compounds, have been proposed to be associated with SIM [2]. One year ago, the Pharmacogenomics Knowledgebase (PharmGKB) published a summary on the *RYR1* gene and analyzed the impact of SVs on drug-induced myopathies following inhalation of volatile anesthetics or treatment with statins [3, https://www.pharmgkb.org/gene/PA34896]. The *RYR1* gene (OMIM *180901) encodes the Ca^{2+} release channel of the sarcoplasmic reticulum in skeletal muscles, also known as ryanodine receptor isoform 1 (RYR1). The RYR1 channel and the voltage-dependent L-type calcium channel Cav1.1 are the two principal channels involved in the excitation-contraction coupling in skeletal muscle. SVs in *RYR1* are the primary cause of malignant hyperthermia susceptibility (MHS), an autosomal dominant pharmacogenetic disorder triggered in genetically predisposed subjects by commonly used volatile anesthetics and/or the neuromuscular blocking agent succinylcholine during general anesthesia. Triggering agents cause an altered calcium regulation in muscle cells that result in a hypermetabolic status. A malignant hyperthermia attack, unless immediately recognized and treated, is often fatal. The MHS status can be diagnosed by an *in vitro* test, based on the differential contractile response of normal and MHS muscles to caffeine and halothane. Protocols for contracture testing of human skeletal muscle have been developed by the European [4], and North American [5]. Malignant Hyperthermia Groups, namely, *in vitro* contracture test (IVCT) and caffeine halothane contracture test (CHCT), respectively. Moreover, *RYR1* SVs associated or possibly associated with MHS status have been identified in patients who experienced exertional or stress-induced rhabdomyolysis [6,7] and in patients with several distinct skeletal muscle disorders [8]. Furthermore, it has been suggested that *RYR1* SVs are also involved in the development of SIM [9] associated with the risk of MHS [10-13]. In fact, some patients who exhibited myotoxic effect following statin treatment have been diagnosed with MHS by IVCT [10-12], indicating an alteration of calcium homeostasis induced by statin therapy. Five *RYR1* SVs have been identified, each in one SIM case [9,14]. The p.Arg614Cys substitution has already been demonstrated to be causative of MHS (www.emhg.org), while the other SVs have been already reported in MHS patients or are of uncertain pathogenicity. Moreover, a transgenic mouse model of MHS, harboring the missense mutation Tyr524Ser in the RYR1 channel, exhibited a malignant hyperthermia-like response to simvastatin in a dose-dependent manner [15]. The drug-induced hypermetabolic response detected in this mouse model can explain many clinical symptoms associated with SIM in humans, i.e., muscle fatigue, cramping, CK increase. Therefore, some MHS genotypes were suspected to predispose patients to SIM, with statins unmasking latent *RYR1*-related myopathy.

The association of SIM with MHS status and with *RYR1* SVs indicated that at least a proportion of patients who experienced SIM should be considered as candidates for MHS and non-triggering anesthetic agents should be used when necessary until

definitive diagnostic IVCT and possibly genetic analysis can be performed.

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Cite this article

Carsana A (2017) Statin-Induced Myopathy, RYR1 Gene Sequence Variations and Association with Malignant Hyperthermia Susceptibility. Int J Clin Anesthesiol 5(3): 1074.