FEATURED NEW INVESTIGATOR

Translational insight into statin-induced muscle toxicity: from cell culture to clinical studies

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Statins are lipid-lowering drugs used widely to prevent and treat cardiovascular and coronary heart diseases. These drugs are among the most commonly prescribed medicines intended for long-term use. In general, statins are well tolerated. However, muscular adverse effects appear to be the most common obstacle that limits their use, resulting in poor patient compliance or even drug discontinuation. In addition, rare but potentially fatal cases of rhabdomyolysis have been reported with the use of these drugs, especially in the presence of certain risk factors. Previous reports have investigated statin-induced myotoxicity *in vivo* and *in vitro* using a number of cell lines, muscle tissues, and laboratory animals, in addition to randomized clinical trials, observational studies, and case reports. None of them have compared directly results from laboratory investigations with clinical observations of statin-related muscular adverse effects. To the best of our knowledge this is the first review article that combines laboratory investigation with clinical aspects of statin-induced myotoxicity. By reviewing published literature of *in vivo*, *in vitro*, and clinically relevant studies of statin myotoxicity, we aim to translate this important drug-related problem to establish a clear picture of proposed mechanisms that explain the risk factors and describe the diagnostic approaches currently used for evaluating the degree of muscle damage induced by these agents. This review provides baseline novel translational insight that can be used to enhance the safety profile, to minimize the chance of progression of these adverse effects to more severe and potentially fatal rhabdomyolysis, and to improve the overall patient compliance and adherence to long-term statin therapy. (Translational Research 2014;164:85–109)

Abbreviations: ABCG2 = adenosine triphosphate-binding cassette G2; CK = creatine kinase; CoA = coenzyme A; EMG = electromyographic; FDA = Food and Drug Administration; F-PP = farnesyl pyrophosphate; G-PP = geranylgeranyl pyrophosphate; HMG = hydroxy methylglutaryl; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; MDR = multidrug resistance gene; MRP = multidrug resistance-associated protein; OATP = organic anion-transporting polypeptide; ^{31}P-MRS = ^{31}P magnetic resonance spectroscopy; PDE = phosphodiester; RD = rhabdomyosarcoma; SLCO = solute carrier organic anion gene; SNP = single nucleotide polymorphism; TUNEL = terminal deoxynucleotidyl transferase mediated 2′-deoxyuridine 5′-triphosphate nick end labeling; UGT = uridine diphosphate glucuronosyltransferase

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Statins, among the most commonly prescribed drugs worldwide, are lipid-lowering agents used to prevent and treat cardiovascular and coronary heart diseases.[1] Statins act primarily by inhibiting the synthesis of mevalonate, a rate-limiting step in cholesterol biosynthesis, leading to a reduction in plasma low-density lipoprotein cholesterol levels (LDL-C).[2] In addition to their cholesterol-lowering effects, a number of other clinical benefits, so-called pleiotropic effects, have been recognized.[3] The most important pleiotropic effects of statins include improvement of endothelial function, inhibition of vascular inflammation, thrombogenesis, and low-density lipoprotein cholesterol oxidation, stabilization of atherosclerotic plaques, immunomodulatory actions, and antiproliferative effects on smooth muscle cells.[1,4,5]

Mevastatin was the first statin discovered by Akira Endo and his colleagues in 1970s from the mold *Penicillium citrinum*.[6] Currently, 7 statins are available for clinical use. The first statin approved by the U.S. Food and Drug Administration (FDA) was lovastatin in 1987, followed by simvastatin, 1988; pravastatin, 1991; fluvastatin, 1994; atorvastatin, 1997; rosuvastatin, 2003; and pitavastatin, 2009.[7] Another agent, cerivastatin, was approved by the FDA and launched in the United States in January 1998, but was subsequently withdrawn from the market in August 2001 because of spontaneous adverse event reports of rhabdomyolysis.[8] Between 1998 and 2001, 40 cases of cerivastatin-induced myotoxicity were reported to be fatal.[7]

Statins are generally well tolerated. Common adverse events include dyspepsia, flatulence, constipation, generalized gastrointestinal discomfort, elevated transaminase levels, myalgia, headache, sleep disorders, and central nervous system disturbances.[9,10] Muscle complaints constitute the major adverse effect limiting the use of statins.[11] The severity of these complaints ranges from myalgia and limb weakness to myopathy consisting of necrosis of skeletal muscle fibers often accompanied by elevated serum creatine kinase (CK) or more pronounced and potentially fatal breakdown of skeletal muscles (rhabdomyolysis), with the release of myoglobin and subsequent renal damage.[3]

The purpose of this review is to provide translational insight into the pathophysiological mechanisms, diagnostic measures, and predisposing factors of statin-associated muscle toxicity both *in vivo* and *in vitro*. To the best of our knowledge, this is the first review that combines laboratory methods and findings with clinical aspects of statin-induced myotoxicity. We aim to translate this important drug-related problem to establish a clear picture of proposed mechanisms and risk factors, and to describe the diagnostic approaches currently used for evaluating the degree of muscle damage induced by these agents. This work provides translational insight that can be used to enhance safety profiles, to minimize the chance of progression of these adverse effects to more severe and potentially fatal rhabdomyolysis, and to improve the overall patient compliance and adherence to long-term statin therapy.

DEFINITION AND INCIDENCE OF STATIN-INDUCED MYOTOXICITY

In clinical practice, 5%–10% of patients receiving statins develop myopathy. This side effect has been underestimated in randomized controlled trials,[12] probably because of the exclusion of high-risk patients, such as patients with a history of muscular symptoms or CK elevations, and the omission of mild symptoms in patient interviews and clinical trial adverse event reports.[13]

According to the US National Lipid Association Statin Safety Assessment Task Force,[14] a meta-analysis of 21 clinical trials found that myopathy, defined as muscle symptoms and CK levels greater than a 10-fold upper limit of normal, occurs in 5 patients/100,000 person-years. Rhabdomyolysis, defined as CK levels more than 10,000 IU/L or CK levels more than 10× the upper limit of normal, plus elevation in serum creatinine or requirement for hydration therapy, occurs in 1.6 patients/100,000 person-years.[15-17]

The terminology used to describe muscle-related side effects is significantly inconsistent and confusing. In an attempt to address these inconsistencies, the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute adapted the definitions presented in Table I.[16,18,19]

MECHANISMS OF STATIN-INDUCED MYOTOXICITY

Many hypotheses have been proposed to explain statin-induced myotoxicity. One theory states that blocking cholesterol synthesis by hydroxy methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors reduces the cholesterol content of skeletal muscle cell membranes, making them unstable.[20] The membrane lipids are in dynamic equilibrium with plasma lipids. Low plasma cholesterol levels are usually associated with reduced intracellular cholesterol and may result in decreased membrane lipid content. This, in turn, may cause physical alteration of membrane fluidity and reduce cell proliferation.[9]

There is also a postulation that statin-induced myotoxicity is not a result of decreased cholesterol synthesis, but rather a reduction in the availability of the isoprenoid cometabolites farnesyl pyrophosphate (F-PP) and geranylgeranyl pyrophosphate (G-PP)[18] (Fig 1).[21] The reduction in the synthesis of F-PP and G-PP