Pharmacological Reports
2011, 63, 859–866
ISSN 1734-1140

Review

Statin-induced myopathies

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Abstract:
Statins are considered to be safe, well tolerated and the most efficient drugs for the treatment of hypercholesterolemia, one of the main risk factor for atherosclerosis, and therefore they are frequently prescribed medications. The most severe adverse effect of statins is myotoxicity, in the form of myopathy, myalgia, myositis or rhabdomyolysis. Clinical trials commonly define statin toxicity as myalgia or muscle weakness with creatine kinase (CK) levels greater than 10 times the normal upper limit. Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure, disseminated intravascular coagulation and death. The exact pathophysiology of statin-induced myopathy is not fully known. Multiple pathophysiological mechanisms may contribute to statin myotoxicity. This review focuses on a number of them. The prevention of statin-related myopathy involves using the lowest statin dose required to achieve therapeutic goals and avoiding polytherapy with drugs known to increase systemic exposure and myopathy risk. Currently, the only effective treatment of statin-induced myopathy is the discontinuation of statin use in patients affected by muscle aches, pains and elevated CK levels.

Key words:
statins, myotoxicity, myalgia, rhabdomyolysis

Abbreviations: CI – confidence interval, CK – creatine kinase, CoQ – coenzyme Q, FDA – US Food and Drug Administration, HMG-CoA – 3-hydroxy-3-methylglutaryl coenzyme A, MRP2 – multidrug resistance protein 2, RD – risk difference per 1000 patients, SLCO – solute carrier organic anion transporter, SR – sarcoplasmatic reticulum, UDP – uridine diphosphate, UGT1 – glucuronosyl-transferase-1, ULN – upper limit of normal, VSMCs – vascular smooth muscle cells

Introduction

Statins are considered to be safe, well tolerated and the most efficient drugs for the treatment of hypercholesterolemia, one of the main risk factor for atherosclerosis, and therefore they are frequently prescribed medications [21, 23].

The 4S study [39] published in 1994 showed that chronic intake of simvastatin significantly reduced mortality in individuals with hypercholesterolemia and coronary heart disease. These data triggered a great interest in statins. Subsequent studies highlighted the benefits of statin treatment in primary and secondary prevention for coronary heart disease and in individuals with normal cholesterol levels [16, 25, 40]. Currently, the role of statins in reducing the risk of cardiovascular disease is well established [39].

According to the World Health Organization definition, adverse drug reactions are any noxious, unintended and undesired effects of a drug, which occur at doses used in humans for prophylaxis, diagnosis or therapy. This definition excludes therapeutic failures, intentional and accidental overdose and drug abuse, adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than the prescribed amount) [50].

Adverse drug reactions account for approximately 5% of all hospital admissions and 5% of all fatalities [19, 27]. Cerivastatin was withdrawn from the market by the US Food and Drug Administration (FDA) in 2001 due to reports of rhabdomyolysis, which was associated with cerivastatin-gemfibrozil combination therapy [43].

Myotoxicity – definition and incidence

The most severe adverse effect of statin therapy is myotoxicity. Its various forms include myopathy, myalgia, myositis and rhabdomyolysis [19] (Tab. 1).

The number of muscle complaint incidences varies between studies mainly due to the contradictory definitions of myopathy. According to the US National Lipid Association Statin Safety Assessment Task Force [33], a meta-analysis of 21 clinical trials providing 180,000 person-years of follow-up found that myopathy, defined by muscle symptoms and creatine kinase (CK) levels above a 10-fold upper limit of normal (ULN), occurs in five patients per 100,000 person-years. Rhabdomyolysis, defined by CK levels above 10,000 IU/l or above a 10-fold ULN with an elevation in serum creatinine or requirement for hydration therapy, occurs in 1.6 patients per 100,000 person-years [26]. Less severe manifestations are much more common. Myalgias with or without CK elevation affect 2–7% of patients, and asymptomatic CK elevation up to 10-fold ULN is noted in 11–63% of patients [2]. One recent cohort study confirmed that the risk of myopathy varies with ethnic group, with Caribbean and black African groups having the highest risks [17].

Myalgias

Symptoms of statin-induced myopathy include any combination of myalgias, muscle tenderness or weakness. Patients describe an aching or cramping sensation in their muscles. Tendon pain and nocturnal leg cramps may also occur [23, 42]. Muscle symptoms are typically more widespread and intense with exercise, and athletes are frequently intolerant to statin therapy. Muscle weakness is usually proximal, but some patients describe difficulty opening jars and snapping their fingers [42]. The incidence of myotoxicity is estimated as 0.1–0.5% in cases of monotherapy and 0.5–2.5% in cases of multiple medications [42]. In randomized control trials, the incidence is approximately 1.5–5% [19, 26].

In a study of 45 patients with statin-associated myopathy, muscle symptoms developed a mean of 6.3 months after statin therapy started and persisted up to 2.3 months after the discontinuation of statin therapy [14]. In the meta-analysis by Kashani et al. [20], myalgias were reported in 21 studies of 48,138 patients. There was an insignificant trend toward a higher inci-

Tab. 1. Type of statin-induced myopathies and associated symptoms

Type	Symptoms	References
Myopathy	Any muscle disease; myalgia, muscle tenderness, weakness, cramps, CK elevation	2, 17, 19, 26
Myalgia	Muscle aches, CK normal	2, 19, 20, 23, 42
Myositis	Inflammation, CK elevation	2, 19, 21, 23
Rhabdomyolysis	Above symptoms and CK elevation, renal insufficiency	2, 13, 19, 26

dence of myalgia in statin-treated patients compared with placebo-treated patients. When myalgia was evaluated among individual statins, only atorvastatin had a significantly higher risk difference per 1,000 patients (RD) when compared to placebo (5.1% *vs.* 1.6%; p = 0.04; RD, 31.9; 95% CI, 2.1 to 61.6). The higher rate of myalgia in clinical practice may reflect the tendency to exclude potentially statin-intolerant patients and those with risk factors for muscle toxicity (polypharmacy, elderly patients, renal or hepatic impairment) from randomized controlled trials [18].

The frequency of muscle symptoms associated with statin therapy was evaluated in the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, an observational study conducted in an unselected population of 7,924 hyperlipidemic patients receiving high-dose statins in an outpatient setting in France [4]. Muscle-related symptoms were reported by 832 patients (10.5%), which is a rate at least 2 times higher than that observed in clinical trials involving statins (1–5%) [46]. The number of patients reporting muscle-related symptoms was the highest in those receiving simvastatin (18.2%), followed by atorvastatin (14.9%), pravastatin (10.9%) and fluvastatin (5.1%). The potential triggering factor for muscle symptoms was noted by 41% out of the 832 patients with muscle-related symptoms. Physical exertion (53%) and taking new medications (30%) were reported as causes of myalgia. The median time to the onset of muscle-related symptoms was one month after the initiation or intensification of statin treatment. Heaviness, stiffness and cramps were reported by 57.9% of patients. Weakness or a loss of strength during exertion was experienced by 26.6% of patients. Widespread pains were reported by 60.1% of patients. Pain was more common in the lower extremities, including thighs and calves [46].

On the basis of the PRIMO study, it was concluded that the frequency and disruptiveness of muscle-related symptoms due to high-dose statin therapy had been underestimated [4]. The risk factor analyses confirmed that a personal or family history of muscular symptoms, cramps, hypothyroidism and elevated CK levels are major risk factors for muscle-related symptoms during high-dose statin therapy. It is relevant to note that the PRIMO study was an observational, non-randomized study that relied on a chronological occurrence of statin treatment and muscle-related pain [4]. The incidence of myopathy, defined as diffuse muscle symptoms such as pain, tenderness and weakness with elevated CK, in patients treated with statins estimated from cohort studies supported by randomized trials was 11 patients per 100,000 person-years [26].

It is worth mentioning that muscle weakness and abnormal electromyographic findings can be associated with underlying neuromuscular disease; e.g., paraneoplastic polymyositis, amyotrophic lateral sclerosis, Kennedy's disease and muscle phosphorylase b kinase deficiency [10]. These conditions usually affect people over 60 years of age. CK levels in these cases are usually above 1,000 U/l [10].

Raised creatine kinase levels

Clinical trials commonly define statin-induced toxicity as myalgia or muscle weakness with CK levels greater than 10 times the ULN [10, 42, 47]. In the meta-analysis of 16 studies including 41,457 patients by Kashani et al. [20], CK elevation was not significantly higher in patients treated with statins [20]. In a cross-sectional study of 136 patients with lipid-lowering drug-induced myopathies, Vladutiu et al. [48] reported a higher prevalence of underlying metabolic muscle diseases than expected in the general population. This study and other reports suggest that some patients who were thought to have a statin-induced myopathy had pre-existing myopathies. CK levels are not routinely measured before statin therapy begins. Patients are encouraged to report myalgia by a physician warning or the product information sheet. When CK levels are elevated, the statin is usually withdrawn, although it is difficult to determine whether statin therapy or another cause is to blame [48].

Rhabdomyolysis

Rhabdomyolysis is the most severe adverse effect of statins, which may result in acute renal failure, disseminated intravascular coagulation and death.

According to Guyton [13], the mortality risk from rhabdomyolysis (estimated to be 0.3 per 100,000 person-years) is outweighed by the reduction in mortality by all causes observed in statin trials (360/100,000 person-years). According to the FDA, the rate of fatal rhabdomyolysis is 0.15 per 1 million statin prescriptions (ranging from 0 with fluvastatin to 3.16 with

cerivastatin) [20, 43]. The meta-analysis by Kashani et al. [20] confirms the rare incidence of rhabdomyolysis with currently available statins and a 12-fold increased risk with cerivastatin, which was withdrawn in 2001. Rhabdomyolysis was reported in 20 studies including 68,110 patients and was not more common in the statin-treated group, with a relative risk (RR) of 1.09 (95% CI, 0.65 to 1.83). Statin-induced rhabdomyolysis is related to drug interactions in approximately 60% of cases. More importantly, it has not been shown that concomitant use of fibrate and statins would result in a higher rate of rhabdomyolysis than therapy with statin alone [20].

On the contrary, Law and Rudnicka [26] showed that the incidence of rhabdomyolysis was approximately ten times higher when concomitant statin therapy with gemfibrozil was used [26]. It has been also reported that the incidence of rhabdomyolysis among patients taking statins (other than the withdrawn cerivastatin) in 2 cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, as supported by data from randomized controlled trials [26].

According to Law and Rudnicka [26], the incidence of rhabdomyolysis may be higher for patients taking lovastatin, simvastatin and atorvastatin due to their metabolism by the CYP3A4 isoform of cytochrome P450, which is inhibited by many commonly used drugs, than for fluvastatin (oxidized by CYP 2A9) and pravastatin (not oxidized by CYP 2A9). These data are supported by the rate of rhabdomyolysis noted by the FDA Adverse Effects Reporting System (AERS), which was approximately four times higher for monotherapy with lovastatin, simvastatin and atorvastatin than for monotherapy with pravastatin and fluvastatin [6]. Multiple case reports document interactions of statins with various medications that resulted in myopathy. Rosuvastatin has been shown to cause myopathy in combination with sildenafil [37]. Symptoms improved several days after statin therapy was stopped. Moreover, co-administration of colchicine with multiple statins [11] and atorvastatin with fusidic acid [30] also induce myopathy.

Mechanisms of myotoxicity

The exact pathophysiology of statin myopathy is not fully known. Multiple pathophysiological mechanisms may contribute to statin myotoxicity. This review focuses on some of them (Tab. 2).

Membrane excitability

Statins are selective 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and usually do not have affinity for other enzymes or receptor systems [8]. Cholesterol synthesis is a diverse and multistage process [44]. HMG-CoA reductase is a key enzyme in this process and catalyzes the conversion of HMG-CoA into mevalonate. Mevalonate is not only a precursor of cholesterol but also of a number of isoprenoid intermediary metabolites. Isoprenoids play important roles in the posttranscriptional lipid modification of proteins, such as prenylation. Isoprenoid deficiency may impair synthesis of transfer RNAs, glycoproteins, the electron transport chain proteins heme A and ubiquinone (coenzyme Q10) [42] and small G-proteins involved in cell signaling and the attenuation of apoptosis [2].

Membrane cholesterol modulates membrane fluidity in various tissues including skeletal muscles. Altering membrane fluidity may affect ion channels like sodium, potassium and chloride channels, which modify muscle membrane excitability. Chloride channels in skeletal muscles control resting membrane potential and membrane repolarization [42]. Animal studies showed a dose-dependent reduction of membrane chloride conductance in simvastatin-treated rats, whereas the resting membrane potential was not affected [38]. Chronic treatment of simvastatin in rabbits led to a membrane hyperexcitability similar to that observed in muscle myotonia associated with impaired chloride conductance [42].

Tab. 2. Mechanisms of myotoxicities

Type of mechanism	References
Membrane excitability	38, 42
Mitochondrial function	24, 32, 36
Ubiquinone depletion	5, 20, 23, 32, 34, 42, 51
Calcium homeostasis	23, 28, 29, 36, 42, 44, 48
Apoptosis induction	9, 12, 22, 31, 34, 42, 44
Genetic determinants	21, 23, 31, 36, 41, 45, 47–49

Mitochondrial function and ubiquinone depletion

The mitochondrial theory is based on the fact that statins inhibit the synthesis of mevalonate, a precursor of both cholesterol and coenzyme Q (CoQ10), and states that the statin-induced CoQ10 deficiency is involved in the pathogenesis of statin myopathy [21, 32, 42]. CoQ10 is an essential cofactor of the electron transport chain and an important antioxidant in mitochondria and lipid membranes [36]. The depletion of CoQ10 in myocyte mitochondria may disturb cellular respiration and consequently cause muscle-related toxicities including rhabdomyolysis [7, 36]. The effect of statin therapy on intramuscular levels of CoQ10 is not clear, and data on intramuscular CoQ10 levels in symptomatic patients with statin-associated myopathy are scarce. Mitochondrial function may be impaired by statin therapy [35], and this effect may be exacerbated by exercise [32]. However, data derived from animal and human studies are inconsistent in this regard. In a study in which muscle biopsy specimens were taken from 18 patients with statin drug-related myopathy, only two had mild signs of mitochondrial dysfunction [24]. However, two years later, another study of a subgroup of 16 patients receiving 80 mg simvastatin/day showed a reduction in intramuscular CoQ10 concentrations [32]. CoQ10 supplementation may raise the circulating levels of CoQ10, but data on the effect of CoQ10 supplementation on myopathic symptoms are still inconsistent [5, 20, 23, 32, 34, 51].

Impairment of calcium homeostasis

Animal models have been used to show that statins decrease strength and increase cytosolic Ca^{2+} by elevating both mitochondrial Ca^{2+} permeability and Ca^{2+} release from the sarcoplasmic reticulum (SR) [23, 36] and reducing Ca^{2+} ATPase (SERCA) activity in the SR [36]. Lorkowska et al. [29] revealed that some isoprenoids inhibit L-type Ca^{2+} channels in vascular smooth muscle cells, which could explain the statin-induced Ca^{2+} increase in the endothelium [29, 44]. In *in vitro* studies, simvastatin at therapeutic concentrations caused a large calcium release from intracellular stores into the cytoplasm in myofibers with a weak Ca^{2+} efflux through the permeability pore [42, 48]. This impaired Ca^{2+} homeostasis leads to mitochondrial membrane depolarization. Statin-induced Ca^{2+} release from the SR is indirectly triggered by caffeine or 4-chloro-*m*-cresol. Moreover, it has been showed that the massive release of Ca^{2+} with chronic statin administration in humans can easily account for symptoms of myalgia or cramps [28].

Induction of apoptosis

Apoptosis is a programmed cell death that is regulated and executed *via* activation of specific signaling pathways [9]. It has been reported in *in vivo* and *in vitro* studies that statins can trigger skeletal muscle apoptosis and myopathy *via* their pleiotropic properties [12, 42, 44]. This dose-dependent process has been observed in vascular smooth muscle cells (VSMCs) [12, 35], endothelial cells [35], rheumatoid synovial cells, pericytes, cardiac myocytes and several cancer cells [9]. Statin-induced apoptosis is dependent on a decrease in the translocation of *RhoA* and *Rac1*, but not *Ras*, from the cytosol to the membrane [9]. Statins have been proven to reduce protein synthesis and the growth, fusion and differentiation of myoblasts, suggesting they might impair the regenerative capacity of muscle *in vitro* [42]. However, in *in vitro* studies, statin-induced apoptosis was inhibited by CoQ [36] or bicarbonate [22]. Statin-induced apoptosis in skeletal myoblasts and myotubes is associated with elevated levels of cytosolic Ca^{2+} [9, 34]. The process results from the depletion of isoprenoids, which in turn might decrease protein geranylgeranylation and/or farnesylation that could lead to elevated levels of cytosolic Ca^{2+} and activation of the mitochondrial-mediated apoptotic signaling cascade [9, 31]. It has been suggested that statin-induced damage is associated with the rise in caspase-3 levels as an early measure of apoptosis. Nevertheless, it has still not been established whether statins induce caspase-3 activity *in vivo* 24 h after statin administration [34].

Genetic determinants

The risk of statin-induced myotoxicity increases in combination therapy with drugs metabolized by cytochrome P-450 [23, 36]. It has been suggested that the pathogenic background of statin- and other drug-induced myopathies involves the inhibition of the glucuronidation pathway, a common metabolic pathway for statin biotransformation. Cytochrome P-450 enzymes oxidize most statins in Phase I metabolism. Polymorphisms in uridine diphosphate (UDP)-glu-

curonosyl-transferase-1 (UGT1) modify statin derivatives in phase II of metabolism. Polymorphisms in the solute carrier organic anion (SLCO) family of membrane transporters are genetic variations associated with statin-induced myotoxicity and alter the cellular uptake of statins [21]. Vladiutiu et al. [48] showed that 10% of patients with myotoxicity were heterozygous or homozygous for disease-causing mutations; e.g., myoadenylate deaminase deficiency, McArdle disease and carnitine palmitoyl transferase II deficiency [23, 48]. Moreover, a case report of statin-induced mitochondrial encephalopathy, lactic acidosis and stroke-like episode (MELAS) syndrome was described by Thomas et al. [45]. A recent SEARCH study [41] revealed a strong association between instances of simvastatin myopathy and common variants in a single gene, *SLCO1B1*, which encodes the organic anion-transporting polypeptide OATP1B1 responsible for regulating the hepatic uptake of statins [31, 41, 47, 49]. A variety of single nucleotide polymorphisms and disease-causing mutations may contribute to the genetic predisposition for statin myopathy [47, 49].

Risk factors

The prevention of statin-related myopathy involves using the lowest statin dose required to achieve therapeutic goals and avoiding polytherapy with drugs known to increase systemic exposure and myopathy risk [18].

The identification of patients with an elevated risk of statin-induced myopathy is substantial. On the basis of the PRIMO study, the major risk factors for muscle symptoms during high-dosage statin therapy are a personal or family history of muscle symptoms, cramps, hypothyroidism and elevated CK levels [4]. In a QResearch cohort study [17], men prescribed corticosteroids had a two-fold risk increase and women a three-fold increase. Women with type 1 diabetes had a five-fold increased risk of myopathy. The study showed that female patients are affected by myopathy more than male patients if they have risk factors like hypothyroidism, type 1 diabetes, chronic liver disease and treated hypertension [17].

Patient-related risk factors for statin-related myotoxicity include female gender, low body mass index, concomitant treatment with certain cytochrome P450 inhibitors, a decline in renal and hepatic function, changes in albumin and α-1 glycoprotein levels with subsequent changes in free concentrations levels of statins [18].

Statin myopathy is dose-related. An increase in statin dose and statin systemic exposure magnifies the risk of CK elevation and muscle toxicity [18]. However, the risk of statin-associated rhabdomyolysis is not related to the magnitude of the reduction in LDL cholesterol [1]. A lower dose of a more potent statin may have less of a myopathy risk than a higher dose of a less-potent statin [18]. It has also been proposed that the risk of myopathy is much higher with lipophilic statins because of their ability to enter muscle cells and to alter membrane structure. Lipophilic statins are transported by passive diffusion; however, hydrophilic HMG-CoA reductase inhibitors (pravastatin) require multidrug resistance protein 2 (MRP2) [36]. Moreover, the ability to induce side effects may be related to the longer elimination half life of atorvastatin (15–30 h) with respect to fluvastatin (0.5–2.3 h) [8, 23].

Conclusions

The above-mentioned mechanisms of statin-induced myotoxicity are hypothetical, and most of them are based on *in vitro* and experimental studies on animals. Statins were shown to have pleiotropic effects [44]; however, more studies on myotoxicity are required to understand these mechanisms in humans. Once understood, it will be easier to develop preventative measures or to invent a new generation of lipid lowering medications. Currently, the only effective treatment of statin-induced myopathy is the discontinuation of statin use in patients affected by muscle aches and pains and elevated CK levels. Occasionally, clinicians use low-dose statins, alternate-day dosing or twice-weekly dosing with statins with a longer half life [15]. It has been also suggested that vitamin D can be used to prevent and treat myopathies, but its efficacy has not been proven in any clinical trial [3, 15].

Additionally, serum CK level is the most commonly used marker of the exacerbation of myopathy with exercise and statin usage; however, it is not a reliable indicator of statin-induced muscle damage. Further research with a more direct muscle assessment is re-

quired, especially in cases of severe statin-associated muscle damage and low CK levels.

Moreover, statins themselves may not have a direct toxic effect on muscle fibers without enhancement by cytochrome P450 inhibitors. Thus, the risk factors for myotoxicity should be considered prior to treatment with medications of similar pharmacokinetics and pharmacodynamics.

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Received: December 9, 2010; **accepted:** March 3, 2011.