Models of Lipid-Lowering Drug-Induced Myopathies

Subjects: Toxicology

Contributor: Krzysztof Jagla

Drug-induced myopathies are classified as acquired myopathies caused by exogenous factors. These pathological conditions develop in patients without muscle disease and are triggered by a variety of medicaments, including lipid-lowering drugs (LLDs) such as statins, fibrates, and ezetimibe.

Keywords: statins ; fibrates ; ezetimibe ; zebrafish ; muscle ; myotoxicity ; side effects of hyperlipidaemia treatment

1. Introduction

Drug-induced myopathies are classified as acquired myopathies caused by exogenous factors. These pathological conditions develop in patients without muscle disease and are triggered by a variety of medicaments, including lipid-lowering drugs (LLDs), neuroleptics, anticancer agents, antibiotics, corticosteroids, antivirals, and many others [1][2][3]. Drug-induced myopathies arise as a side effect of drug therapy intended to target a medical condition not directly related to muscle symptoms. These kinds of myopathies are manifested by muscle disorders which can be defined by the common term myotoxicity. This problem affects many groups of patients and its consequences could be fatal.

The term drug-induced myopathy is very broad, covering an extensive spectrum of symptoms ranging from myalgia (muscle pain or weakness without creatine kinase, CK, elevation), myositis (muscular complaints with CK elevation) to extremely serious symptoms associated with necrosis or rhabdomyolysis. The mechanisms underlying drug-induced myopathies are very diverse and can include direct muscle damage caused by mitochondrial injury or immune-mediated inflammatory damage [4].

Hyperlipidaemia is the most common dyslipidaemia. It is a pathological condition manifested by abnormal amounts of lipids (e.g., triglycerides, cholesterol, fatty phospholipids). Hyperlipidaemia is defined as abnormally elevated levels of any or all lipids and lipoproteins in the blood. This includes hypercholesterolaemia characterized by high cholesterol levels in the patient's blood. Dyslipidaemia therapies are based on the use of various LLDs which include statins, fibrates, niacin, bile acid sequestrants, ezetimibe, lomitapide, phytosterols, omega-3 supplements, and PCSK9 inhibitors [5][6]. Widely used LLDs, intended to reduce the risk of cardiovascular diseases (CVD), have been the most commonly reported drugs to be associated with the adverse effects manifested by myotoxicity [3][7].

2. Pathological Mechanisms Underlying Lipid-Lowering Drug-Induced Myopathies

2.1. Statins

The pharmacological function of statins (e.g., simvastatin, SIM, and atorvastatin, ATV) is the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), which is the key enzyme of cholesterol synthesis in the mevalonate pathway in the liver (PubChem compound identification numbers are summarized in Table S1). The inhibition of HMGCR has an impact on the intermediates of cholesterol synthesis such as coenzyme Q10 (CoQ10; ubiquinone), geranylgeranyl pyrophosphate (GGPP), and farnesyl pyrophosphate (FPP) [8][9][10].

Recent studies revealed that statins, despite lowering the cholesterol level, could have additional benefits, e.g., anti-inflammatory, antioxidant and immunomodulatory effects, inhibition of platelet activation, regulation of pyroptosis (a highly inflammatory form of lytic programmed cell death), increase in plaque stability, and improvement of renal function [11][12][13][14][15][16][17]. Nevertheless, some of the patients experienced side effects connected with muscle symptoms. It has been shown that there are several mechanisms involved in statin-induced myopathies.

It was suggested that in endothelial cells the function of the membrane-bound proteins could be changed after SIM treatment because the accompanying decrease in the level of cellular cholesterol, leading to increased cell membrane fluidity (since cholesterol is an important component of the cell membrane) [18][19]. The membrane fluidity changes and

modification of muscle susceptibility occur as a result of the statin-dependent reduction of cholesterol. Modifications of membrane structure can influence the function of sodium, potassium, and chloride channels, resulting in muscle cell damage and leading to myopathies [20]. For example, studies on L6 rat myoblasts showed that SIM impaired the function of Na^+/K^+ and Na^+/Ca^{2+} ATPase, which are crucial for maintaining the cellular membrane electrical potential [21].

Impaired prenylation (post-translational modification of protein requiring intermediates of the cholesterol biosynthesis pathway, which can be inhibited by statins) disturbs proteins' ability to anchoring to membranes, leading to their deactivation [22][23][24]. Prenylated proteins are translocated from the cytoplasm to cellular membranes, where they interact with other important proteins. Almost 2% of cellular proteins undergo the covalent attachment of prenoid lipid adducts, farnesyl or geranylgeranyl [25][26][27][28]. Therefore, impaired protein prenylation might be a potential statin-induced myotoxicity mechanism (reviewed by [8]). Many proteins, e.g., lamins and small GTP-binding proteins (such as Rab, Ras, and Rho), are substrates for prenylation [29]. For example, prenylated Ras is involved in cellular proliferation and adhesion. Mullen et al. (2010) reported that disruption of cholesterol synthesis by SIM did not change the cellular CoQ10 level [30]. However, the Ras prenylation by geranylgeranyl pyrophosphate was decreased. Since only geranylated Ras can be attached to the sarcolemma of muscle cells, where it plays an important role in cell survival, inhibition of this process could explain the myotoxic mechanism of statins [31], reviewed by [8]. Additionally, ATV decreases the cholesterol level in C2C12 cells, which impairs the translocation and function of the glucose transporter GLUT4 [32], reviewed by [8]. Statin-induced inhibition of dolichols, other intermediates of the mevalonate pathway involved in protein N-glycosylation, may also lead to myopathy [20][33][34].

The observations of a decreased level of CoQ10 in statin-treated skeletal muscle of human patients and rodent models had led to the conclusion that statins may influence mitochondrial function, affect muscle function and disrupt its morphology [35][36]. Based on these studies, additional mechanisms of statin-induced myopathy can be directly or indirectly linked to mitochondria. The significant decrease of CoQ10 level, which is a key electron transporter localized in the inner membrane of mitochondria, and caused by lower cholesterol level, might result in the reduction of ATP production and cell damage [37], as reviewed by [8]. A decreased CoQ10 level in skeletal muscle in statin-treated patients and higher lactate/pyruvate ratio are considered as indicators of abnormal mitochondrial function [36][38][39].

Recent studies revealed that statin treatment in rats can cause mitochondrial membrane depolarization and a calcium wave (a localized increase of Ca^{2+}) in skeletal muscle sarcoplasm with subsequent calcium release from the sarcoplasmic reticulum (SR). Ca^{2+} outflow from SR (so-called Ca^{2+} sparks) is a result of dissociation of ryanodine receptor 1 (RyR1), a process which is involved in pro-apoptotic signalling [36][40]. Numerous studies showed that an increased level of Ca^{2+} in cells is a major factor in apoptosis. Therefore, calcium regulation mechanisms, such as this mediated by RyR1, can be a crucial player in the regulation of apoptosis [41][42][43][44]. In contrast, no Ca^{2+} sparks were observed in cardiac myocytes after statin treatment, the reason being that RyR2, not RyR1, is present in cardiomyocytes [36][40][45].

It worth to noting that positive family history is a common risk factor for statin intolerance, as reviewed by [46]. Several studies show a significant association between muscle pain and single nucleotide polymorphisms (SNPs) in patients who have received statin treatments (e.g., SIM, and cerivastatin, CER) [47][48][49][50][51][52], as reviewed by [46]. For example, genome-wide scans of patients have revealed a strong association between SIM-induced myopathy and c.521T>C [53]. This association is a result of a nearly complete linkage imbalance between non-coding SNP in the *SLO1B1* and c.521T>C SNP linked with a reduction in the cholesterol-lowering effect of SIM, reviewed by [54]. These data suggested that statin-related myopathy may be a result of different genetic mechanisms [47].

In general, statins are well tolerated by patients. However, muscle-related side effects of statin treatment are frequently reported. Interestingly, one of the rare statin-associated side effects is immune-mediated necrotizing myopathy (IMNM) [55], reviewed by [56]. IMNM is diagnosed by the presence of muscle fibres necrosis and degeneration, and is correlated with CK level and muscle strength [56][57]. Additionally, based on presence of myositis-specific antibodies (MSAs), IMNM can be divided into: (1) anti-HMGCR, (2) anti-SRP (signal recognition particle), and (3) antibody-negative myopathy [58].

The pathogenesis of anti-HMGCR myopathy is poorly understood. Nevertheless, it has been proposed that statins could initiate autoimmunity by increasing the expression and availability of the autoantigen HMGCR. Additionally, statins could bind to HMGCR, causing its conformational changes, and alternate processing by antigen-presenting cells [59][60][61][62] reviewed by [56]. The in-vitro studies showed that anti-HMGCR and anti-SRP autoantibodies are involved in atrophy of muscle fibres and increase the *MAFbx* (muscle atrophy F-box; atrogin-1) and *Trim63* (*MuRF1*; *muscle RING finger 1*) transcription. Additionally, high levels of the inflammatory cytokines TNF and IL-6 were associated with IMNM. Furthermore, the observed decreased production of IL-4 and IL-13 resulted in impaired myoblast fusion [63].

2.2. Fibrates

Other LLDs, fibrates (e.g., fenofibrate, and clofibrate), decrease plasma triglyceride and cholesterol levels via several mechanisms comprising induction of lipoprotein lipolysis, stimulation of cellular fatty acid uptake, and reduction of triglyceride synthesis in the liver. They can also increase the removal of low-density lipoprotein (LDL) particles, and lower neutral lipid exchange between very-low-density (VLDL) and high-density (HDL) lipoproteins. They also increase HDL level and stimulate reverse cholesterol transport [64].

Fenofibrate and clofibrate, agonists of peroxisome proliferator-activated receptor α (PPARα), are currently used to treat dyslipidaemia. However, treatment using a highly selective PPARα inhibitor in rats could result in skeletal muscle degeneration and necrosis [65][66]. The inhibition of the PPARα receptor by fenofibrate leads to increased β-oxidation and oxidative stress in skeletal muscle, as a consequence [66][67]. Furthermore, the additional oxidative stress may also result in mitochondrial dysfunction, because fenofibrate inhibits complex I (the first protein complex of the respiratory chain, which catalyses the transfer of electrons from nicotinamide adenine dinucleotide phosphate (NADPH) to CoQ10) [68]. A study by Pettersen et al. (2012) revealed that skeletal muscle degeneration correlates with increase in acyl-CoA oxidase (AOX) mRNA expression, which is involved in the PPARα signalling pathway. Surprisingly, no correlative increase of palmitoyl-CoA β-oxidation was detected. The histological analysis showed that necrosis took place only in type I muscle fibres. In these muscles, β-oxidation is the source of the energy; therefore its inhibition by fibrates leads to cell death [69].

The fibrate-induced skeletal muscle myotoxicity mechanisms involve the activation of PDK4 (pyruvate dehydrogenase kinase 4). Fibrates (e.g., bezafibrate, clofibrate, and ciprofibrate) inactivate pyruvate dehydrogenase complex, which is responsible for catalysis of irreversible decarboxylation of pyruvate to acetyl-CoA. As a result, limited oxidation of glucose and three-carbon compounds, and enhanced fatty acid oxidation are observed in cells [70][71]. One of the fibrates, gemfibrozil, has been suggested to inhibit the glucuronidation pathway, which increases the risk of muscle disorders. Furthermore, increased risk of muscle injury and fibrate concentration could result from another gemfibrozil-mediated pathway by inhibition of cytochrome P_{450}2C8 (CYP2C8) activity [72][73]. Other fibrates, such as fenofibrate, have not demonstrated a significant effect on glucuronidation [74][75]. Furthermore, fenofibrate has poor potential to inhibit cytochrome P_{450}3A4 (CYP3A4). However, fenofibrate acid (FA), which is a substrate of CYP3A4, has been reported to inhibit organic anion transporting polypeptide 1B1 (OATP1B1) [74][76][77][78].

2.3. Ezetimibe

Ezetimibe, like statins and fibrates, is successfully used to treat hypercholesterolaemia (Table S1). Ezetimibe's mechanism of action is the selective inhibition of the cholesterol absorption in the intestine by blocking Niemann-Pick C1-Like 1 (NPC1L1) protein transporter, which is present in the enterocyte membrane and plays a key role in cholesterol uptake [79][80][81]. Numerous studies have revealed that ezetimibe, contrary to statins and fibrates, has not been associated with an increased rate of myopathy or rhabdomyolysis, whether used alone or in a combination with statins, as reviewed by [81]. Nevertheless, there have been several case reports of myopathy attributed to ezetimibe, where patients have had an elevated level of CK activity [82][83][84][85][86]. It is known that statins are hydrolysed by cytochrome P_{450} and metabolised by glucuronidation. Since ezetimibe is not metabolised by cytochrome P_{450} and it is extensively glucuronidated, it was proposed that impaired ezetimibe glucuronidation might be responsible for myopathy [87]. Hsiang et al. (1999) suggested that ezetimibe, like statins, might be a substrate for organic anion transporter 2 (OATP2) [88]. Case studies showed that ezetimibe in monotherapy can induce myalgia in patients who suffer from statin-induced myopathy. Ezetimibe could impair fatty acid oxidation as the possible pathology mechanism [84].

3. Models for Study of Lipid-Lowering Drug-Induced Myopathies

The LLD-induced myotoxicity assessments were conducted using a variety of models including cell lines and mammalian organisms (e.g., mouse, rat, goat, rabbit, and dog) (Table 1). Among various LLDs, statins are the most commonly applied in humans for the prevention and treatment of CVD. Therefore this group of drugs gain special attention from researchers [89].

In-vitro research using human and murine cell lines provides new data concerning LLD-induced myotoxicity and confirmed differences in the side effects caused by LLDs belonging to the same group (e.g., statins). This kind of research also helps to examine compounds which could protect cells exposed to LLD treatment. For example, recent studies carried out on mouse C2C12 skeletal muscle cells shed more light on the molecular mechanisms of the cytoprotective effect of geranylgeraniol (GGOH), a mevalonate-derived isoprenoid. GGOH protects cells treated with statins, precisely ATV and SIM, through the inhibition of calpains, which are calcium-dependent, nonlysosomal cysteine proteases [90]. Moreover, these experiments revealed that different statins, depending on the degree of their lipophilicity, cause more (SIM, higher lipophilicity) or less (ATV, lower lipophilicity) myotoxicity manifested in impaired cellular mitochondrial respiration. Notably,

studies conducted on a rodent model of statin-induced myalgia have also confirmed that the administration of GGOH can prevent skeletal muscle fatigue [91].

Studies on cell lines have also provided a lot of valuable information regarding the molecular mechanism of LLDs' mechanism of action, which has proven to be very complex. Specifically, primary human muscle cells exposed to a lipophilic SIM and hydrophilic rosuvastatin (RSV) display various changes in their metabolism, and gene and protein expression profiles (regarding more than 1800 mRNA transcripts and 900 proteins). In addition to its well-documented effects on cholesterol biosynthesis, treatment with both investigated statins causes changes in profiles of eicosanoids secreted by human muscle cells. It also disrupts their proliferation and differentiation. Furthermore, results of the study support the hypothesis that supplementation with omega-n fatty acids (eicosanoids precursors) might be beneficial as a prevention or as a treatment for patients undergoing statin therapy [92].

To meet the needs arising from the necessity to study LLD-induced myotoxicity, researchers continue to refine existing tools and develop new ones. An example is a microphysiological system based on patient-derived myoblasts. The cells form engineered myobundles mimicking the organization and function of native skeletal muscle, allowing for the study of skeletal muscle ex vivo development [93]. The system was used to investigate the statin-associated musculoskeletal symptoms [94]. Statin exposure leads to myotoxicity manifested in the reduction of cells' contractile force, and disruption of sarcomeric actinin organization.

Data gained via in-vitro experiments, despite their undisputed advantages, are limited in terms of predicting in-vivo conditions and are not able to replicate the behaviour of cells in an entire living organism. Therefore, in-vivo studies conducted on more complex model organisms such as a mouse are thought to provide more valuable and reliable information regarding the effects of progression of particular diseases, and their treatment. Osaki et al. (2015) developed skeletal muscle-specific HMGCR knockout mice which were intended to mimic human post-statin myopathy conditions [95]. The generated model exhibited severe myopathy caused by the deficiency of HMGCR enzyme activity and resulting in depletion of mevalonic acid (MVA). In HMGCR knockout mice, induction of skeletal muscle cell membrane damage, myofibrils necrosis, and an elevated serum CK level were observed. Oral administration of MVA revealed that the generated model was completely rescued [95].

As mentioned in the previous chapter, also genetic polymorphisms are risk factors for LLD-induced myotoxicity. Research related to this phenomenon was conducted using transgenic mouse models carrying different slow-channel congenital myasthenic syndrome (SCS) mutations [96]. The results demonstrated that one of the genetic variants of the nicotinic acetylcholine receptor (nAChR) could be related to the onset of statin-induced side effects. The nAChR is a transmembrane glycoprotein expressed in skeletal muscle at neuromuscular junctions (NMJs), which transduces the chemical signal necessary for muscle contraction. Studies revealed that mice expressing a mutant variant of nAChR (SNP rs137852808; αC418W) display impaired neuromuscular transmission upon ATV treatment. The study provides an important clue to explain one of the most common statin side effects regarding neuromuscular problems contributing to muscle pain or weakness [96].

The histopathological changes, comprising hypercontraction and fibre necrosis, in muscle exposed to statins have also been examined using a rat model. Studies on rats have confirmed the distinct susceptibility of skeletal muscle to damage caused by therapy with different statins (more severe in the case of lipophilic SIM and lovastatin (LOV) than hydrophilic pravastatin [PRA]). Moreover, it was also reported that young rats are more susceptible to statin-induced muscle damage than adults [97].

Further investigations conducted on female rats revealed that type II muscle fibres (primarily glycolytic and poor in mitochondria) are most vulnerable to muscle injury caused by statins [98]. However, other research groups using young male rats obtained contrary results. According to their outcomes, the CER-induced myotoxicity affects only type I, but not type II fibres [99]. This suggests that susceptibility to muscle-related side effects induced by LLD therapy depends on additional factors such as age and/or gender.

Studies carried out on a rat model also made it possible to establish some details regarding molecular mechanisms underlying statin-induced myopathy [100]. The obtained results showed that SIM down-regulates PI3k/Akt signalling, and up-regulates FOXO transcription factors. The latter is followed by an increase in the transcription of genes implicated in proteasomal- and lysosomal-mediated protein degradation, such as *MAFbx*. Studies also revealed impairment of carbohydrate oxidation, the occurrence of oxidative stress, inflammation, and increased plasma CK level. Muscle necrosis appeared in the group of animals exposed to the longest statin treatment [100].

Further, proteomic analyses using a rat model have provided valuable information on the effects of LLDs, represented by statins (ATV, and fluvastatin, FLV) and fibrates (fenofibrate), on the expression profiles of treated skeletal muscle [101]. The mentioned analyses focused on the expression levels of proteins crucial for skeletal muscle functions, such as proteins associated with energy production systems (including oxidative and glycolytic enzymes and CK), heat shock proteins (providing protection against oxidative stress), and proteins that are components of myofibrils. Proteomic examination demonstrated that all treatments induced a general tendency to down-regulation of protein expression. [101].

The rabbit is also one of the animal models used to study myotoxicity phenomena caused by LLD exposure. Studies in this species have confirmed data gained from other models and provided an interesting insight into the muscle pathology induced by LLDs [102][103]. Treatment with statins leads to necrosis and degeneration of rabbit muscle fibres. Ultrastructural examination allowed the accompanying changes to be described in more detail, revealing the presence of autophagic vacuoles and swollen mitochondria, as well as disruption of myofibrils and Z-bands [103].

The goat is gaining acceptance as an established model for biomedical studies and research with environmental relevance. This is mostly related to methane emissions caused by ruminants. Methane is one of the major greenhouse gases and its emission influences the climate. Its enteric formation is a by-product of the digestive process of ruminants and directly results from the activity of anaerobic bacteria. The reduction of methane emission is currently one of the significant challenges worldwide. Various measures are being used for this purpose, including LOV supplementation of animals, such as goats [104]. Therefore, due to the side effects caused by statins, the influence of these compounds on goat skeletal muscle began to be studied [105]. The histology studies revealed the occurrence of LOV-induced goat muscle damage correlated with increasing dosages. Moreover, the proteomic analysis showed that LOV triggers complex modifications to carbohydrate metabolism, energy production, and muscular system development [105]. This shows how important it is to evaluate side effects when studying the use of known substances in new models or for new purposes.

The dog has proven to be an excellent model corresponding to human diseases. Kawata and Yokoi (2019) carried out studies to explain the effects of LOV and fenofibrate on a dog's skeletal muscles [78]. Oral co-administration of LOV and fenofibrate caused skeletal muscle injury. Similarly to other animals tested in this respect, in the skeletal muscles but not in cardiomyocytes, elevated levels of CK and necrosis of skeletal muscle fibres were observed. Also, the conducted research also provides an interesting implication for examination and validation of non-invasive biomarkers of clinical drug-induced side effects. One of the proposed biomarkers of LLD-induced skeletal muscle injury is an increased level of miR-1 in plasma. miR-1 is a representant of microRNA particles, which are small non-coding RNAs, characterized by high stability in blood and muscle expression pattern [78].

The use of a variety of established and reliable animal research models enables the discovery of novel properties of well-characterized compounds, as exemplified by statins. These drugs appear to be a particularly interesting group of LLDs because, in light of unorthodox research on the development of therapies for Duchenne muscular dystrophy (DMD) based on statins, their dual nature regarding their effects on skeletal muscle function has been revealed [106]. DMD is the most common and severe form of lethal muscular dystrophy caused by mutations in the dystrophin gene. SIM seems to have a positive impact on the skeletal muscle of dystrophic (mdx) mice, dramatically reducing damage and enhancing their function. These improvements are accompanied by autophagy activation, a recent therapeutic target for DMD, and less oxidative stress [106].

As stated above, models provided insight into the pathogenesis of LLD-induced myotoxicity. The in-vitro studies and research on mammalian model organisms reveal a wide range of data regarding the treatment of diseases induced by LLDs. Despite the many advantages of in-vitro and mammalian models, their research use has some limitations, e.g., results obtained from in-vitro tests do not always reflect in-vivo processes, and in the case of animal models, the number of individuals in the litter does not allow for reliable statistical analysis. This makes the development of new models and further in-depth research necessary.

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