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Drug-related Myopathies of Which the Clinician Should Be Aware

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Abstract

Many drugs used for therapeutic interventions can cause unanticipated toxicity in muscle tissue, often leading to considerable morbidity. A drug-induced, or toxic, myopathy is defined as the acute or subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase elevation, or myoglobinuria that can occur in patients without muscle disease when they are exposed to certain drugs. A brief review of agents with a known association with myotoxicity and the proposed mechanisms linked to that toxicity is outlined; however, the purpose of this review is to highlight recent discoveries and advances in the field of toxic myopathies that have practical implications for practicing physicians. Because many drug-related myopathies are potentially reversible at early stages, it is important for clinicians to recognize toxic myopathies early in their course to determine when to discontinue therapy and potentially prevent irreversible muscle damage.

Keywords

Toxic myopathy; Drug-induced myopathy; Statin myopathy

Introduction

Many drugs used for therapeutic interventions can cause unexpected toxicity in muscle tissue, often leading to significant morbidity and disability. Myotoxic drugs can cause myopathies through a variety of mechanisms by directly affecting muscle organelles such as mitochondria, lysosomes, and myofibrillar proteins; altering muscle antigens and generating an immunologic or inflammatory reaction; or by disturbing the electrolyte or nutritional balance, which can subsequently impact muscle function. Muscle tissue seems particularly susceptible to drug-related injury because of its mass, high blood flow, and mitochondrial energy metabolism. As many drug-related myopathies are potentially reversible at early stages, it is important that clinicians recognize toxic myopathies early in their course to institute therapy and prevent irreversible damage.

Diagnosis of Drug-induced Myopathies

A drug-induced, or toxic, myopathy is defined as the acute or subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase (CK) elevation, or

myoglobinuria that can occur in patients without muscle disease when they are exposed to certain drugs [1]. Symptoms of myopathy typically occur weeks or months after administration of the drug and usually improve or resolve within weeks after discontinuation of the offending agent. Elevated CK levels are not sufficient for a diagnosis of toxic myopathy, and muscle biopsy is often necessary to document evidence of myotoxicity and eliminate other causes of weakness and/or elevated CK in the differential diagnosis.

Toxic myopathies are often a diagnosis of exclusion, as the differential diagnosis for muscle symptoms can be quite broad. Endocrine disorders such as hypothyroidism, hyperthyroidism, and hyperparathyroidism are common causes of elevated CK and muscle weakness and always should be considered when toxic myopathy is suspected. Similarly, muscular dystrophies such as limb girdle muscular dystrophy, dystrophinopathies, Becker's muscular dystrophy, or Duchenne's muscular dystrophy can also mimic symptoms of drug-induced myopathies. Metabolic disorders such as glycogen or lipid storage diseases, mitochondrial myopathies, and nutritional deficiencies can cause exercise intolerance, elevated CK, myalgias, or weakness. Inflammatory diseases such as polymyositis, dermatomyositis, or inclusion body myositis also should be considered and excluded through muscle biopsy, as these disorders have different therapeutic implications.

Clinical and Histologic Spectrum of Drug-induced Myopathies

The actual incidence of drug-induced myopathy is unclear, primarily because the clinical manifestations of myotoxicity can be variable and not necessarily related to a single agent. Mild symptoms that sometimes occur with drug-induced myopathies, such as fatigue, myalgias, or mildly elevated CK, are usually not reported to the US Food and Drug Administration in a drug's postmarketing period. It stands to reason then that clinical trial estimates of these adverse events are an underestimation of the real world event rate. Similarly, reporting of adverse drug effects is also limited to monotherapies and does not often take into account the wide variety of drug interactions that commonly occur in clinical practice. Drug-related myotoxicities such as rhabdomyolysis or myoglobinuria are more typically reported, as they are more serious medical emergencies. Rhabdomyolysis is a fulminant and acute, necrotizing myopathy that can cause severe pain, muscle swelling and weakness, and elevated serum CK as high as 2000 times the upper limit of normal. It is associated with myoglobinuria (urine that appears dark brown or pink due to the presence of pigmented myoglobin), which can cause acute renal failure and death. If the offending agent is removed and patients are aggressively treated, the muscle typically heals well.

Toxic myopathies can occur from a variety of different mechanisms and types of muscle injury and are typically classified according to the types of injury to the muscle fiber or muscle organelle (Table 1) [1–3]. Myopathies induced by drugs most commonly result in necrosis, vacuolar changes, or mitochondrial dysfunction. Necrotizing myopathies such as those caused by statins lead to necrosis of muscle fibers and secondarily involve inflammatory cells such as macrophages. However, they do not typically demonstrate widespread major histocompatibility complex-1 expression or the primary inflammation by aggressive T lymphocytes that one sees in the immune-mediated inflammatory myopathies that can be induced by D-penicillamine or interferon (IFN)- α . Vacuolar changes and lysosomal accumulations typically occur with colchicine and the antimalarial class of medications, respectively. Mitochondrial dysfunction characterized by ragged red and cytochrome C oxidase-negative fibers occurs with zidovudine toxicity. Still other drugs (eg, ipecac and emetin) can cause disruption of myofilaments or myofibrillar proteins, which can lead to toxic effects in muscle.

Although the broad overview above encompasses many of the recognized agents and the associated mechanisms associated with toxic myopathies, the purpose of this review is to highlight recent discoveries and advances in the field of toxic myopathies that have practical implications for practicing physicians. The greatest emphasis is on recent updates in myotoxicity associated with cholesterol-lowering agents. Muscle diseases related to these agents garner the greatest amount of scientific interest, as evidenced by the recent growing body of literature that expands our understanding of the etiology at a mechanistic level.

Drugs Associated With Myotoxicity

Cholesterol-lowering Drugs

Statins—HMG-CoA reductase inhibitors, commonly referred to as *statins*, are among the most commonly studied and well-recognized myotoxic agents. This is almost certainly a function of the extent to which they are prescribed rather than an inherently higher myotoxicity associated with this drug class itself. Indeed, atorvastatin remained the number-one-selling drug in America in 2009. Despite statins' proven efficacy in reducing cardiovascular morbidity and mortality, estimates suggest that as many as half of patients are noncompliant with these medications after 1 year. Although multifactorial reasons for this noncompliance exist, it has been suggested that most patients discontinue statins because of side effects [4].

What's in a name? There is no standard definition for the various forms of myotoxicity, the most common being myalgia, myopathy, myositis, and rhabdomyolysis. Various groups have provided their own definitions. These are summarized in Table 2 [5•].

The most common muscle-related adverse event resulting from statin use is myalgia, with its incidence reported in randomized controlled trials ranging from 1.5% to 3.0%. A recent 5-year, randomized, placebo-controlled trial of 20,536 patients from the United Kingdom with vascular disease or diabetes found a very low rate of myopathic symptoms on the order of less than 1% [6•]. However, in clinical practice, up to 10% of outpatients receiving statins report muscle pain [7–9]. German investigators sought to find an association between statin use and patient-reported musculoskeletal complaints (in patients ≥ 50 years of age) in a primary care setting while generating a logistic regression model with several covariates associated with such complaints [10]. Statin prescription versus no prescription was an independent variable associated with 1.5-fold odds of musculoskeletal complaints.

Wide variation in definitions, the failure to carefully characterize adverse events reported in the literature, and potential limitations of the US Food and Drug Administration Adverse Event Reporting System all hinder the ability to determine the absolute risks of muscle-related adverse events with use of statins. These limitations notwithstanding, serious muscle toxicity with marketed statins remains rare: myopathy occurs in 5 patients per 100,000 person-years, and rhabdomyolysis in 1.6 patients per 100,000 person-years [7,11,12]. Nevertheless, these estimates translate to a large number of affected individuals, owing to the sheer number of patients taking these drugs.

In this current era of genomic exploration, the authors of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial hypothesized that strong associations would exist between the myopathy associated with high-dose statin regimens and genetic variants, especially those affecting blood statin levels [13•]. This elegant study helped elucidate one explanation for susceptibility to statin myopathy, at least as it relates to simvastatin. Reduced-function single nucleotide polymorphisms (SNPs) of the *SLCO1B1* gene were shown to be associated with statin myopathy, with an impressive OR of 16.9 in homozygotes. This SNP may explain up to 60% of cases of simvastatin-

associated myopathy. Because *SLCO1B1* encodes the enzyme AOTB1B1, which is responsible for liver transportation of statins, this SNP has biological plausibility. Voora and colleagues [14•] extended this observation further to demonstrate that in addition to the association of reduced allele function for this gene and CK elevation, there was also an association between the *SLCO1B1**5 allele and myalgias without CK elevation. Additionally, owing to the fact that patients with this SNP likely will not transport simvastatin to the liver effectively, prescribing physicians are likely to increase the dose prescribed to these patients when their cholesterol profile has not been greatly affected, unknowingly further exacerbating their underlying genetic susceptibility to statin-related myotoxicity. Although these studies touch upon the probable future of genetic testing to be able to help risk stratify patients, this is not the entire story. This particular SNP does not seem to explain statin myopathy across the entire class, as the incidence of myalgias among patients with this SNP taking atorvastatin was higher; however, it did not reach statistical significance. Additionally, pravastatin metabolites were not significantly elevated in patients with the homozygous *SLCO1B1* genotype. Rosuvastatin, fluvastatin, and lovastatin were not investigated. It is likely that other candidate gene SNPs will be uncovered, casting a wider net on our understanding of genetic predisposition to statin myopathy as it relates to each individual statin. As genetic evidence shows that statin myopathy may not be a class effect, it may be worth switching to another statin when one agent is poorly tolerated, especially if the risk–benefit profile favors statin use.

It is worth querying statin users for symptoms of myotoxicity at every visit, especially when seemingly therapeutic statin doses do not seem to lower cholesterol appropriately. Although routine CK monitoring is not necessary in asymptomatic patients, we personally advocate obtaining a baseline CK and asking patients about any weakness or myalgia at each visit. At least one clinical advisory group supports this [15]. Knowing about family history of statin-related muscle symptoms, a history of hypothyroidism, or known elevations in increased CK (with a potential subclinical myopathy) prior to prescribing a statin suggests that clinicians exercise caution in prescribing statins to these patients at significantly elevated risk of statin myalgia. This is supported by findings from the multivariate analysis of the Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Chronic Kidney Disease Stage 3/4 (PRIMO) study [16].

The first reported case of hyaline myopathy presumably unmasked by statins was recently reported [17]. In this case, histologic evidence of subsarcolemmal inclusions resembling those seen in inherited hyaline body myopathy led to the diagnosis. The muscle biopsy was prompted when the patient, who was previously asymptomatic and had no family history of muscle disease, experienced severe debilitating myalgias shortly after starting statin therapy and was found to have an elevated CPK of greater than 4000 IU/L with persistent myalgias and proximal weakness despite statin cessation. His primary care physician had not checked a baseline CPK, so it was unclear if he had subclinical evidence of this underlying myopathy prior to being treated with a statin.

A baseline CPK can be invaluable when trying to discern whether a statin user with mild myalgias and a CPK of 400 IU/L is elevated from a baseline of 40 IU/L or 375 IU/L. Muscle enzyme values, however, may prove to be unreliable measures of muscle injury from statins. For example, it has been shown that patients can have histologically proven statin myopathy even with normal muscle enzymes reflecting muscle injury [18,19]. Because normal ranges for CK are dependent upon gender, exercise, and ethnicity and are necessarily broad, it is possible for a patient to have muscle injury with a result that is within the reference range. Therefore, some investigators advocate serial testing relative to baseline levels as a more effective method for detecting mild increases in CK [20]. Nevertheless, a rise in muscle enzymes compared with the baseline value in the right clinical context can be helpful in

assessing the relative contribution of the statin to the patient's signs and symptoms and in assessing the risk–benefit ratio of continuing statin therapy or trying an alternative strategy. This alternative strategy may involve an every-other-day or once-weekly regimen—strategies that were well-tolerated and reduced low-density lipoprotein in at least two studies but have not yet been shown to reduce cardiovascular events [21•,22•].

An interesting study by Glueck and colleagues [23] prospectively examined the hypothesis that asymptomatic patients with high CK (≥ 250 but < 2500 IU/L) tolerate statins well at doses reducing low-density lipoprotein cholesterol to target (< 100 mg/dL) without development of myalgia or frank myositis. Their study assessed outcomes of three groups of patients referred because of asymptomatic high CK: group 1 ($n=29$) on statins at referral and continued on statins, group 2 ($n=20$) not on statins and started on statins, and group 3 ($n=19$) not on statins and not given statins (all restudied 1 month after entry and then every 3 months). Despite high baseline CK (48 patients with CK 1–5 times the upper limit of normal, 1 patient with CK 5–10 times the upper limit of normal), during follow-up, no patients on statins developed CK greater than 10 times the upper limit of normal (2500 IU/L), none discontinued statins or reduced statin dose because of myalgia or myositis, and there were no reports of rhabdomyolysis. These investigators argue that asymptomatic high pretreatment CK, particularly one to five times the upper limit of normal, should not be an impediment to starting or continuing statins to lower low-density lipoprotein cholesterol.

Statin toxicity can be potentiated by interactions with concomitant medication, including fibrates, which can have a synergistic benefit on cholesterol reduction and reduction of cardiovascular events. To date, no large-scale, prospective, randomized trial of statin–fibrate combination therapy that examines safety and efficacy is available, although one is currently under way. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is evaluating simvastatin–fenofibrate treatment in diabetic patients and should provide further insight on the risk–benefit ratio for patients prescribed this dual therapy [24]. Clinical studies to date have demonstrated that pharmacokinetic interactions between statins and fenofibrates are less pronounced than those between a statin and gemfibrozil.

It has long been thought that lipophilic statins (simvastatin, atorvastatin, lovastatin) are more likely to produce muscular effects than their hydrophilic counterparts (pravastatin, rosuvastatin, fluvastatin) [25]. However, simvastatin, atorvastatin, and lovastatin are metabolized by the hepatic cytochrome P450 3A4 (CYP3A4) enzyme system, whereas pravastatin, rosuvastatin, and fluvastatin do not rely on CYP3A4. This is especially important in patients who have had a kidney transplant or who have an autoimmune disease and who are receiving immunosuppressive drugs and also require a statin. CYP3A4 metabolizes cyclosporine, tacrolimus, and sirolimus, among numerous other drugs. One recent article showed that 25% of new statin users were prescribed a concomitant CYP3A4 inhibitor in the first year of statin therapy [12]. Increased statin concentrations occur with cyclosporin treatment, thus increasing the risk of myopathy [26]. A comparative case series of rhabdomyolysis reports associated with simvastatin and pravastatin was conducted. Spontaneous adverse event reports demonstrated evidence for increased risk of rhabdomyolysis with simvastatin, but not pravastatin [27].

A growing body of literature suggests that statins, in addition to being direct myotoxic agents, may also promote, unmask, or potentiate an underlying autoimmune myopathy, including a newly recognized autoimmune-necrotizing myopathy [28•,29•], dermatomyositis, and polymyositis, in which these diagnoses are supported by histologic findings, often in combination with specific associated autoantibodies. Increasing evidence also indicates that apoptosis is involved in autoimmunity, possibly because of impaired clearance of apoptotic cells, which may in turn incite an autoimmune response. Statins,

particularly simvastatin, have been shown to induce apoptosis in many types of cells, including B lymphocytes, cardiac myocytes, hepatocytes, vascular smooth cells, and human skeletal muscle cells [30]. How statins exert this proapoptotic effect is unknown, but the mechanism may involve protein prenylation, an effect reversible by mevalonate [31].

Red Yeast Rice—Red yeast rice is a bright reddish-purple fermented rice that acquires its color from being cultivated with the mold *Monascus purpureus*. When produced using the “Went” strain of this mold, it contains significant quantities of the HMG-CoA reductase inhibitor lovastatin, which is also known as *mevinolin*, a naturally occurring statin. It is sold as an over-the-counter dietary supplement for controlling cholesterol. This is a popular alternative lipid-lowering therapy tried by many statin-intolerant patients. Several recent studies evaluated the tolerability and efficacy of this substance [32,33]. Halbert and colleagues [34] found red yeast rice to be as tolerable as pravastatin. The most rigorous study was a small, single-site, randomized, clinical trial of red yeast rice that involved patients with dyslipidemia and a history of discontinuation of statin therapy due to myalgias taking 1800 mg of red yeast rice ($n=31$) or placebo ($n=31$) twice daily for 24 weeks. Patients with statin-related myositis or rhabdomyolysis were excluded [32]. All patients were concomitantly enrolled in a 12-week therapeutic lifestyle change program. Red yeast rice and therapeutic lifestyle change were found to decrease low-density lipoprotein cholesterol level without increasing CPK or pain levels and therefore may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy. It is unclear if patients who had symptoms related to lovastatin use (which is bioidentical to red yeast rice) were as likely to tolerate red yeast rice as patients intolerant to other statins.

Ezetimibe—Although it has a different mechanism of action to lower cholesterol than its statin counterparts, ezetimibe as mono-therapy and in combination with statins has been shown to be associated with myotoxicity. Compelling evidence from most of the data recently reviewed showed that adverse effects associated with ezetimibe use were uncommon and mild without having been associated with serious clinical outcomes [35]. In most studies, ezetimibe has not been associated with increased rates of myopathy or rhabdomyolysis, whether used alone or in combination with statins, although there have been case reports of myopathy attributed to its use.

HIV Therapy

As the use of zidovudine has fallen dramatically, there are fewer reports of toxic myopathy associated with HIV medications. Nevertheless, highly active antiretroviral therapy and HIV are also reported in association with skeletal myopathy and mitochondrial abnormalities on muscle biopsy [36]. This is in contrast to mitochondrial disorders associated with nuclear or mitochondrial DNA mutations, in which patients may present with constellations of dysfunction in metabolically active tissues, including the brain and skeletal muscles. Chronic progressive external ophthalmoplegia is a mitochondrial syndrome with gradual onset of ptosis and ophthalmoparesis [37]. Thus far, phenotypes resembling genetic mitochondrial disorders have not been reported in association with mitochondrial toxicity acquired from disease or drugs. Three cases of HIV-infected patients with long exposure to highly active antiretroviral therapy who developed clinical syndromes resembling those of chronic progressive external ophthalmoplegia were recently reported, adding to the growing literature of HIV-related myopathies in the context of the illness and the related therapy [38].

Antiviral Therapy

Interferon—Type I IFNs are common treatments for several diseases, including multiple sclerosis. Although many studies have implicated type I IFNs in the production of

autoantibodies and the development of certain autoimmune disorders, IFN- β had not been described in association with dermatomyositis prior to the recent report by Somani and colleagues [39]. Microarray studies of muscle biopsy specimens from patients with dermatomyositis demonstrate a robust type I IFN-induced gene expression profile. The essential role of plasmacytoid dendritic cell precursors, together with augmented type I IFN production, suggests a key role for type I IFNs in dermatomyositis. This case report of dermatomyositis exacerbated or induced by IFN- β therapy for multiple sclerosis provides support that demonstrates enhanced type I IFN signaling in this patient. Immunohistochemical staining of skin biopsy specimens for myxovirus-resistance protein A (a surrogate marker for cutaneous type I IFN signaling) showed increased staining that correlated temporally with IFN- β treatment and subsequent disease activity. In vitro treatment with IFN- β of peripheral blood mononuclear cells isolated from this patient revealed enhanced type I IFN signaling assessed by IFN-induced gene expression profiles.

Clevudine—Clevudine is a pyrimidine nucleoside analogue antiviral drug that was recently introduced to treat hepatitis B. Although it is not currently marketed in the United States, it is approved in South Korea and the Philippines. It has been associated with skeletal muscle toxicity in some patients receiving therapy [40]. A recent report in seven such patients demonstrated that all patients had been treated for more than 8 months. Slowly progressive proximal muscle weakness was the main reported symptom in all patients. Markedly elevated CK in addition to electromyographic changes was observed. Muscle biopsies revealed predominantly necrosis with ragged red fibers, cytochrome C oxidase-negative fibers, and type II fiber atrophy. Molecular studies demonstrated that mitochondrial DNA was depleted. This is the first report of clevudine-related myopathy.

Rheumatologic Agents

Antimalarials—Chloroquine and hydroxychloroquine are among the most commonly used agents in dermatologic and systemic manifestations of autoimmune diseases such as dermatomyositis and systemic lupus erythematosus. A prospective study of myopathy induced by antimalarial agents previously conducted by Casado and colleagues [41] suggested serial muscle enzyme screening of patients on these therapies as a way to identify patients at risk. Dr. Jeffrey Callen has extensive experience with antimalarial use for dermatologic diseases and with the use of a prospective study, Callen and colleagues [42] did not find an association between elevated serum muscle enzymes and underlying antimalarial agent-related myopathy in patients taking chloroquine or hydroxychloroquine. Instead, this paper suggests empiric discontinuation of antimalarials in any patient with suspected antimalarial agent-related myopathy.

Immunosuppressants

Glucocorticoids: Widely prescribed agents for a multitude of diseases, glucocorticoids are among the most recognized myotoxins, although the mechanism responsible for this toxicity has not been completely elucidated. The incidence of muscle disease has been reported to be as high as 50% of patients on long-term, high-dose glucocorticoid therapy [43,44]. A recent review focused on one potential mechanism of glucocorticoid myopathy: glucocorticoid-induced apoptosis [45]. Steroid myopathy is often characterized by muscular atrophy, which is believed to be due to suppressed protein synthesis and growth, enhanced proteolysis, and apoptosis induction. Perhaps a better understanding of these mechanisms can lead to alleviation of this side effect from a life-altering, often life-saving medication.

Leflunomide: There was one recent case report of suspected leflunomide-related myopathy that resembled polymyositis in a patient with rheumatoid arthritis [46]. Because concomitant inflammatory myopathies are very rare in patients with rheumatoid arthritis, disease-

modifying agents or biologic therapy should be suspected potential etiologies when elevated CK levels are observed, or when patients report muscle-related symptoms such as weakness or myalgias. This is the first reported case of myopathy associated with leflunomide of which we are aware. It must be added to the ever-growing list of potential myotoxic agents. In this instance, knowing that the two underlying autoimmune diseases (rheumatoid arthritis and polymyositis) rarely travel in pairs should prompt the prescribing physician to suspect a drug-related myopathy over a de novo inflammatory muscle disease. Leflunomide myopathy should be suspected particularly in cases in which transaminases are elevated and are not corrected by cholestyramine, which would suggest that they are of skeletal muscle rather than liver origin.

Tumor necrosis factor- α inhibitors: There are scattered reports of tumor necrosis factor- α inhibitors, including adalimumab, associated with muscle toxicity. A case of severe myalgia associated with adalimumab in a patient with Crohn's disease was recently reported [47]. The patient reported generalized severe pain in her upper and lower extremities. Interestingly, she had been treated previously with infliximab. The infliximab was stopped due to lack of efficacy for her Crohn's symptoms; however, no associated muscle-related symptoms were present. Although infliximab also should be considered for its causal role, infliximab-delayed reactions typically occur several days after an infusion; in this patient, infliximab therapy was suspended 8 weeks before the myalgias occurred. The onset and resolution of the signs and symptoms, while not implicitly suggesting causality, suggest a reasonable temporal sequence following drug initiation and discontinuation and imply that adalimumab was the most likely cause of the myalgias.

Voriconazole

Voriconazole is a new triazole antifungal agent that is now considered the treatment of choice for invasive aspergillosis. Although drug-induced myopathy is well-recognized with other triazole agents, especially in combination with statin therapy, it had not been reported previously with voriconazole. A recent case report detailed a seemingly causal link with myopathy and voriconazole in a transplant recipient—a patient interestingly with a prior history of probable statin-induced myopathy [48]. This patient developed severe generalized weakness with marked elevation of muscle enzymes and edema-like signal on short tau inversion recovery sequence MRI after starting voriconazole for treatment of invasive aspergillosis. Her symptoms resolved and her CK normalized upon drug discontinuation.

Conclusions

Although most clinicians are aware of the myotoxic potential of many drugs, the exact mechanisms and the patients at risk have not been understood previously. As our technological sophistication expands, so too does our understanding of not only the etiology, but also the at-risk patient. Modeling therapy and anticipating untoward side effects on a predictive rather than a reactive model of care is desirable and may soon be a reality.

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Table 1

Types of drug-induced myopathies

Type of myopathy	Histologic findings	Drugs involved
Necrotizing myopathy	Scattered necrotic fibers invaded by macrophages; absence of widespread MHC-1 upregulation	HMG-CoA reductase inhibitors (statins), fibrates, alcohol
Inflammatory myopathy	Non-necrotic muscle cells surrounded and invaded by T lymphocytes and macrophages; MHC-1-expressing fibers	Statins, D-penicillamine, interferon- α , procainamide
Mitochondrial myopathy	“Ragged red” or “ragged blue” fibers, COX-negative fibers, increased lipid accumulation	Zidovudine, germanium
Antimicrotubular myopathy	Lysosome accumulation, autophagic vacuoles	Colchicine, vincristine
Lysosomal storage myopathy	Storage of myeloid structures within lysosomes in the form of autophagic vacuoles	Chloroquine, hydroxychloroquine, quinacrine, perhexiline, amiodarone
Myofibrillar myopathy	Disruption of Z discs, breakdown of myofilaments, accumulation of myofibrillar proteins	Emetine, ipecac
Type II muscle fiber atrophy	Atrophy of type II fibers	Corticosteroids

COX cytochrome C oxidase; MHC major histocompatibility complex

Table 2

Various proposed definitions for statin-related muscle disease

Clinical term	ACC/AHA/NHLBI	NLA	FDA
Myopathy	Any disease of the muscle	Myalgia (muscle pain and soreness), weakness or cramps, and CK >10 times ULN	CK ≥10 times ULN
Myalgia	Muscle ache/weakness in absence of CK increase	Not defined	Not defined
Myositis	Muscle symptoms with elevated CK	Not defined	Not defined
Rhabdomyolysis	Muscle symptoms with significant CK elevation (usually >10 times ULN) and creatinine elevation (with brown urine/urine myoglobin)	CK >10,000 IU/L or CK >10 times ULN and increased CK or medical intervention with intravenous hydration	CK >50 times ULN and evidence of organ damage (eg, renal insufficiency)

ACC American College of Cardiology; AHA American Heart Association; CK creatine kinase; FDA US Food and Drug Administration; NHLBI National Heart, Lung, and Blood Institute; NLA National Lipid Association; ULN upper limit of normal

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