REVIEW

Toxic myopathies

Mamatha Pasnoor[a], *Richard J. Barohn*[a,b], *and Mazen M. Dimachkie*[a]

Purpose of review
Our aim is to highlight major advances reported in the last few years in drug-induced muscle toxicity.

Recent findings
Our focus is on myopathies induced by statins and immune checkpoint inhibitors with a brief overview of rare steroid myopathies. Statin muscle injury is frequently because of direct toxicity rather than an autoimmune mechanism. Laboratory testing and muscle pathologic features distinguish these two conditions. Statin-associated necrotizing autoimmune myopathy (SANAM) is associated with an autoantibody in 66% of cases targeting the HMGCR enzyme. The later autoantibody is a marker for necrotizing autoimmune myopathy, regardless of statin exposure. In SANAM, MHC-I antigens are expressed on the surface of intact muscle fibers. Genetic HLA loci predispose patients exposed to statins to immunologic toxicity. SANAM requires long-term therapy with multiple immunosuppressive therapies. Immune checkpoint inhibitors are powerful emerging therapies for advanced cancer that pause a novel therapeutic challenge.

Summary
This review is focused on statins, the most prevalent myotoxic drug class. In addition, we examine the accumulating body of evidence of muscle injury and its management with immune checkpoint inhibitors. We anticipate the reader to become more knowledgeable in recent discoveries related to these myotoxic drugs, and their mechanisms of action and management.

Keywords
corticosteroid, immune checkpoint inhibitors, myopathy, statin, statin-associated necrotizing autoimmune myopathy

INTRODUCTION

Many substances including commonly prescribed medications can produce adverse effects on muscle [1–4]. Alcohol has been recognized to cause muscle weakness since the middle of 19th century [5]. Adverse effects of medications on muscles have been described mostly within the last 50 years. Cholesterol-lowering medications, particularly the statins [3,6–9,10▪] have been the most commonly prescribed drugs that have been described to cause a myopathy in recent years. Medications can have a direct or indirect adverse effect on the muscle. Direct effect can be focal as might occur secondary to drug being injected into tissue, or generalized. Indirect toxic effects may result from the agent creating an electrolyte imbalance or inducing an immunological reaction. Novel cancer therapies such as immune checkpoint inhibitors may trigger a powerful immune system activation that targets the central or peripheral nervous systems including immune skeletal and/or cardiac muscle disease. Clinical manifestations of toxic myopathies range from muscle pain to more serious muscle damage leading to rhabdomyolysis [1,11]. Although some categories of drugs are associated with specific forms of myopathies, a drug can cause more than one type of myopathy. History of drug use is important in the evaluation of patients presenting with various muscle disorders, and an understanding of the pathophysiology of drug-induced myopathy is useful in the management of these patients. In this update, our focus is on the widely used statins but we will also discuss steroid myopathy and review myotoxicity of immune checkpoint inhibitor use. For a more comprehensive description of other agents that can cause toxic myopathy, the reader is referred to this prior review by the same authors [12].

[a]Neuromuscular Division, Department of Neurology and [b]Research Institute, Heartland Institute for Clinical and Translational Research, University of Kansas Medical Center, Kansas City, USA

Correspondence to Mamatha Pasnoor, MD, Associate Professor, Department of Neurology, University of Kansas Medical Center, 3901 Rainbow Blvd, Mail Stop 2012, Kansas City, KS 66160, USA.
Tel: +1 913 588 6970; fax: +1 913 588 0609;
e-mail: mpasnoor@kumc.edu

Curr Opin Neurol 2018, 31:575–582
DOI:10.1097/WCO.0000000000000606

KEY POINTS

- This article provides important and latest updates to toxic myopathy including information on immune checkpoint inhibitors.
- Immune checkpoint inhibitors have transformed the care and prognosis of cancer, however, they also cause weakness of muscles through various mechanism.
- Statins are the prevalent myotoxic drug class.

CLINICAL PRESENTATION

Clinical manifestations of drug-induced myopathy are often indistinguishable from those of myopathies because of other causes, as well as from idiopathic forms. Clinical manifestations can be varied and with combination of various symptoms including diffuse myalgia (muscle pain and stiffness) without any other neurologic signs, painless proximal myopathy (weakness), painful myopathies, focal myopathy with focal area of damage because of injections, myokymia or rhythmic rippling of muscles, mitochondrial myopathy associated with inhibition of mitochondrial DNA and characterized by ragged red fibers, rhabdomyolysis with myoglobinuria and malignant hyperthermia (Table 1).

PATHOPHYSIOLOGY/PATHOGENESIS

The pathophysiological mechanisms are diverse and in many cases unclear. This is mediated through direct or indirect effects on muscle. Although direct effects can be focal or generalized, indirect toxicity can occur secondary to the drug causing an immunological reaction or electrolyte imbalance. Other mechanisms include specific lysosomal disruptions and autophagic dysfunctions with amphiphilic drugs, inducing oxidative stress such as with alcohol or triggering apoptosis or necrosis-mediated cell death pathways. On the basis of pathogenic mechanisms, eight main categories of toxic myopathies are recognized [3,4]: necrotizing myopathy; amphiphillic myopathies; antimicrotubular myopathy; mitochondrial myopathy; inflammatory myopathy; hypokalemic myopathy and steroid myopathy/critical illness myopathy; unknown (Table 2).

Table 1. Malignant hyperthermia

Susceptibility genes	Inheritance patterns
Ryanodine receptor	Autosomal dominant
SCN4A sodium channel	Autosomal dominant
CACNL2A calcium channel	Autosomal dominant
CACNA1S calcium channel	Autosomal dominant
Carnitine palmitoyltransferase II	Autosomal dominant
Dystrophin	X linked recessive
Myotonin protein kinase	Autosomal dominant
CLCN1 chloride channel	Autosomal dominant
Perlecan	Autosomal recessive

The various genetic conditions associated or predisposed to develop malignant hyperthermia are shown. Reproduced with permission from [3].

Necrotizing myopathy

Introduction

A number of drugs can cause a generalized necrotizing myopathy with cholesterol-lowering drugs

Table 2. Toxic myopathies

Pathogenic classification	Drugs
Necrotizing myopathy	Cholesterol-lowering agents, especially statins (SANAM) Immune checkpoint inhibitors Cyclosporine [13,14] Labetolol [15] Proprofol [16,17] Alcohol [18,19]
Amphiphillic	Chloroquine [20,21] Hydroxycholoroquine [22] Amiodarone [23,24]
Antimicrotubular	Cochicine [25–27] Vincristine [28]
Mitochondrial myopathy	Zidovudine [2,29] Other HIV-related antiretrovirals [30]
Inflammatory myopathy	Cholesterol-lowering agents, especially statins (SANAM) Immune checkpoint inhibitors L-tryptophan [31,32] D-Penicillamine [33] Cimetidine [34] Phenytoin [35] Lamotrigine [4] Alpha-interferon [36,37] Hydroxyurea [4] Imatinib [38]
Hypokalemic myopathy	Diuretics Laxatives Amphotericin Toluene abuse Licorice Corticosteroids [39] Alcohol abuse [19]
Critical illness myopathy	Corticosteroids [40] Nondepolarizing neuromuscular-blocking agents [39]
Unknown	Omeprazole [41] Isotretinoin [42] Finasteride [43] Emetine [44]

The classification of toxic myopathies based on the pathogenic mechanism is presented.

Table 3. Comparison of University of Kansas Medical Center's statin-associated necrotizing autoimmune myopathy group with prior literature

	Grable-Esposito *et al.*, 2010	KU
Cases	25	11
Mean age of onset (years)	64.7	55
Female/male ratio	1.1/1	2.6/1
Phenotype	Proximal arm and leg	Proximal leg mainly
Bulbar symptoms	3	2
Weakness progression after stopping statins for	>1 month	>2 month
Mean creatine kinase	8203	5700
Autoimmune d/o and abnormal labs	Hashimoto thyroiditis ANA (2)	- Jo1 (1)[a], ANA (1) and RF
Number of immunosupressive agents used	22	10

Comparison of the clinical, laboratory and treatment of University of Kansas Medical Center's SANAM patients with Grable-Esposito *et al.*'s patients. SANAM, statin-associated necrotizing autoimmune myopathy group. Reproduced with permission from [12].
[a]Without evidence for interstitial lung disease.

being the major cause of this type of myopathy [45,46]. Other agents include the immunophilins (cyclosporine and tacrolimus), rarely the antihypertensive agent labetalol and propofol.

Statins including lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and cerivastatin inhibit HMGR, the rate-limiting enzyme in cholesterol synthesis. Cholesterol-lowering agents including statins, fibric acid derivatives, niacin and ezetimibe may cause a toxic myopathy. In addition to toxic necrotizing myopathy, which improves with discontinuation of the offending drug, recent evidence indicates that statins can alternatively trigger an autoimmune myopathy that progresses for 1–2 months despite statin cessation. We refer to this autoimmune disorder as statin-associated necrotizing autoimmune myopathy (SANAM) [47].

Statins

Clinical presentation

Statin myopathy has a pleomorphic presentation. Although myalgias, weakness or asymptomatic elevation of creatine kinase levels [6] do occur with statin exposure, severe necrotizing myopathy is rare and multifactorial and in extreme cases may be complicated by rhabdomyolysis, myoglobinuria and renal failure.

In statin necrotizing myopathy, immediately stopping the offending agent is of critical importance. Proximal weakness may develop after periods of statin exposure ranging from weeks to even years. Weakness in SANAM usually progresses beyond 2 months following statin cessation [47]. In contradistinction, patients with statin-induced toxic necrotizing myopathy stabilize in strength and markedly improve within 2–3 months of stopping their statin therapy. A retrospective chart review performed at The University of Kansas Medical Center showed 11/18 (61%) patients on statins having SANAM and 7/18 (39%) with toxic necrotizing myopathy (Table 3). Mean SANAM age of onset was 55, with more women than men, and disease duration upon presentation was 2–12 months. Proximal leg weakness was the most common presentation with SANAM, few had proximal arm weakness and neck flexor weakness. Though others described dysphagia, respiratory or bulbar dysfunction was not seen in our case series [48].

Laboratory features, electrophysiology and muscle imaging

In SANAM, creatine kinase is usually elevated at least 10 times above the upper normal limit [47]. The amount of muscle damage is proportional to the degree of serum creatine kinase elevation and it may provide a useful clue as to the pathophysiology of acute severe muscle weakness. In general, creatine kinase in SANAM does not exceed 27 000 to 30 000 IU/l but is much higher in cases of acute toxic rhabdomyolysis. Despite overlap in creatine kinase values in milder toxic cases and SANAM, creatine kinase elevation beyond 30 000 IU/l supports rhabdomyolysis.

Electromyography (EMG) showed myopathic units in all SANAM cases with fibrillation potentials seen in nine patients, pseudomyotonia seen in five. Pseudomyotonic discharges on electromyography are not seen in rhabdomyolysis and lend further support to SANAM.

Other features that would suggest SANAM include MHC-I expression on the surface of intact myofibers and detection of HMGR autoantibodies in

two-thirds of SANAM. The most frequently identified autoantibodies in necrotizing autoimmune myopathy (NAM) target the HMCR, and these are detectable in 40% of NAM cases [49▪]. Second most common are SRP autoantibodies in 16% of NAM (unrelated to statin exposure) and the rest of NAM cases (44%) are idiopathic. It is noteworthy that a third of NAM that harbor HMGCR autoantibodies have never been exposed to statins, suggesting that HMGCR antibodies are markers of NAM rather than being specific to statin-mediated immunologic dysfunction.

Muscle MRI generally shows a predilection for posterior thigh and hip muscles as well as the medial thighs. A combination of active disease (increase in short tau inversion recovery signal) and lack of fibrotic changes (normal T1 signal) is usually indicative of likely treatment response to immunotherapies.

Although it was reasonably assumed that SANAM in conjunction with HMGCR antibodies is immune-mediated, recent evidence suggests that there is an increased risk of cancer [50]. Therefore, screening for cancer is important to detect malignancy, which affects up to 11.5% of seropositive SANAM cases and is even higher (21.4%) with seronegative NAM.

Histopathology

Muscle histology in SANAM reveals marked muscle fiber necrosis with prominent phagocytosis and some basophilic regenerating fibers and at times mild lymphocytic inflammation. MHC-I is overexpressed on the surface of myofibers of SANAM cases but not in toxic necrotizing myopathy or in acute rhabdomyolysis. In the toxic statin-mediated necrotizing myopathy and in addition to necrotic muscle fibers, lipid-filled vacuoles within myofibers and cytochrome oxidase-negative myofibers may be rarely and inconsistently appreciated [51].

Pathogenesis

In SANAM, Needham *et al*. [52] reported an upregulation of MHC-I expression even in nonnecrotic fibers of patients presenting with progressive necrotizing myopathy after statin use. Mammen and colleagues demonstrated that statins induce antibody to 200 and 100 kD autoantigen. They then discovered that statins upregulate expression of HMGCR and that the autoantibody in SANAM targets the HMGCR [53]. NCAM-positive regenerating muscle cells expressed high levels of HMGCR, which may then sustain the immune response even after statin discontinuation [51,53–55].

More recently, several studies have demonstrated an association in up to 70% of SANAM cases with HLA-DRB1∗11: 01 across ethnically diverse populations [56,57]. As this HLA haplotype can be seen in 7–15% of the general population, it makes this a scientifically interesting observation as a risk factor but is of limited diagnostic utility in SANAM.

Treatment

Multiple and long-term immunosuppressive agents are required in most SANAM cases. For more detailed discussion, the reader is referred to our prior publication [15].

Other cholesterol-lowering drugs

Niacin, ezetimibe, colevesam, fibric acid derivatives such as fenofibrate and gemfibrozil are other cholesterol-lowering agents. Although monotherapy with each of these has been reported to cause myopathy in few case reports and review articles [58], the link between these drugs' exposure and development of myopathy is best established for gemfibrozil. With each agent, the risk of myopathy appears to increase with concomitant statin therapy.

Gemfibrozil interferes with statin metabolism, increases statin plasma concentrations and is associated with increased risk of rhabdomyolysis compared with fenofibrate when coadministered with a statin [59]. Patients may present with myalgias, creatine kinase elevations or weakness that may start few weeks after starting the medications and sometimes may develop several years after drug initiation. Stopping the drug leads to stabilization then progressive improvement in the ensuing 2–3 months.

Drug-induced inflammatory myopathies

Cholesterol-lowering agents were discussed in the prior section on necrotizing myopathies but can at times be associated with the disease of polymyositis or even dermatomyositis. L-tryptophan-induced eosinophilia myalgia syndrome is of historic interest (Table 1). For more detailed discussion, the reader is referred to our prior publication [12].

Immune checkpoint inhibitors

Clinical features

Pembrolizumab and nivolumab are antibodies that bind the programmed cell death 1 (PD-1) receptors found on the surface of T-cells. They block binding of tumor-secreted PD-1 ligands to the PD-1 receptor. Tremelimumab is an antibody to programmed death ligand 1. Ipilimumab and durvalumab are antibodies to cytotoxic T-lymphocyte-

associated antigen 4. Collectively these novel cancer immunotherapies are referred to as immune checkpoint inhibitors (ICI). ICIs have transformed the care and prognosis of many types of advanced cancer.

With ICI restorating antitumor activity of host T cells, rare off-target autoimmune effects have become an emerging concern [60]. Although most reactions are mild and nonspecific, the incidence of ICI-associated central and peripheral neurological adverse reactions is 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with combination therapy [61▪▪]. More specifically, the frequency of myositis with nivolumab is 0.15% being fatal in 0.01% of cases but when nivolumab is combined with ipilimumab, these rates increase to 0.24 and 0.03%, respectively [62▪▪].

Onset of severe ICI-triggered weakness may be acute within 5 days of starting these therapies or delayed by up to 19 weeks [61▪▪], with arm and/or leg proximal muscles [62▪▪,63] weakness. Bulbar or ocular dysfunction suggest associated myasthenia gravis.

Off-target effect sometimes affects more than one neurologic system. In a 2017 case report and literature review, 5/12 ICI-induced myasthenia gravis cases had serum creatine kinase level elevation between 1200 and 8729 IU/l, and biopsy showed myositis in one case [64]. Since then another case was reported with head and neck cancer [63] who was treated with nivolumab and developed within 3 weeks de novo myositis (creatine kinase 2593 IU/l) with acetylcholine receptor (AChR) antibody positive myasthenia gravis in the setting of proximal weakness and ptosis. Two melanoma patients treated with combination ipilimumab and nivolumab developed myositis with rhabdomyolysis, and fatal myocarditis [62▪▪] characterized by early progressive and refractory cardiac electrical instability with remarkably preserved cardiac function. Severe autoimmune polymyositis with respiratory dysfunction leading to death occurred in the setting of combination tremelimumab and durvalumab therapy [65]. Postmortem evaluation demonstrated predilection of lymphocytic infiltration to the diaphragm.

Laboratory features

In ICI myositis cases, creatine kinase is typically more than six times and up to 100 times elevated [62▪▪] above the upper normal limit. AChR antibody is elevated in most but not all myasthenia gravis cases and in seronegative cases, single fiber EMG is helpful [64]. EMG may show scattered myopathic motor unit action potentials.

Histopathology

Pathologically, the two fatal myocarditis cases had lymphocytic myocarditis and myositis, characterized by abundant CD4 and CD8 positive T cell and macrophages in both the heart and skeletal muscles [62▪▪]. Postmortem diaphragm muscle predominant lymphocytic infiltration was noted in a respiratory presentation case [33].

Pathogenesis

Off-target immune activation mediates ICI-triggered myositis and other autoimmune complications. Two hypotheses have been proposed: 'hidden autoimmunity' and molecular mimicry [61▪▪]. In the former, ICI uncovers a genetic predisposition to an autoimmune disease that was hidden by previously competent immune tolerance. Another mechanism that interferes with immune self-tolerance is molecular mimicry, mediated by antibodies targeting tumor cells that in turn cross-react with central or peripheral nervous system antigens.

Treatment

Specific treatment guidelines [66▪▪] have been developed based on toxicity grades for prompt multispecialty case review and symptom-directed evaluation and management with a proposed decision tree for ICI discontinuation either temporarily or permanently [63].

In addition to ICI cessation, severe cases require high-dose oral or intravenous corticosteroids for the treatment of myositis. In milder myasthenia cases, lower dose steroids are reported to be beneficial [64]. For those with associated myasthenic crisis, plasma exchange is indicated and in hemodynamically unstable cases, intravenous immunoglobulins should be considered. The decision to resume or continue ICI treatment is complex, requires input to the oncology team from neurologic specialty and is tailored based on severity of adverse event and cancer response.

There is limited retrospective data that suggests that most patients (75%) with preexisting autoimmune disease experienced a disease flare after exposure to ICI [67]. Most flares were managed with corticosteroids whereas 16% required other immunosuppressive therapies. Though adverse events improved in more than 50% of cases without discontinuation of ICI therapy, three patients died of these adverse events. Depending on assessment of ICI risks, benefits and alternatives, ICI therapy may be a reasonable option when coupled with careful and vigilant monitoring. This would best serve to aggressively and promptly recognize and manage autoimmune flares in advanced cancer patients needing these life-saving therapies.

Myopathies because of impaired protein synthesis or increased catabolism

Steroid myopathy

Clinical features

Chronic, high-dose corticosteroid exposure is rarely associated with an increased risk of steroid myopathy [68]. More commonly, acute onset of severe generalized weakness can occur in patients receiving high dosages of intravenous corticosteroids with or without concomitant neuromuscular blocking agents or sepsis.

Chronic steroid myopathy manifests as proximal muscle weakness and atrophy [68–70], and Cushingoid appearance [71]. Fluorinated glucocorticoid are more likely than nonflourinated agents to cause muscle weakness [72] and women appear to be at higher risk than men.

Laboratory and electrophysiological features

Serum creatine kinase is normal but glucocorticoid treatment may lower potassium thereby leading to weakness. Although in steroid myopathy motor and sensory nerve conductions are normal and fibrillation potentials are absent [38,73,74], EMG may show subtle myopathic changes, but is typically normal.

Histopathology

Muscle biopsy reveals atrophy of primarily type 2 fibers, especially the fast-twitch, glycolytic type 2B fibers [71], which explains the paucity of changes on EMG as this test primarily activates type 1 fibers at low level of effort. Lipid droplets are commonly noted in type 1 fibers.

Pathogenesis

Exact pathogenesis of corticosteroid myopathy is not known, but could be the result of decreased protein synthesis, increased protein degradation, alterations in carbohydrate metabolism, mitochondrial alterations, or reduced sarcolemmal excitability [71].

Treatment

Reduction in the dose, tapering to alternate-day regimen, or switching to nonflourinated steroid along with a low carbohydrate diet and exercise to prevent concomitant disuse atrophy are major modes of therapy [71,72]. If weakness develops in the course of chronic high-dose steroids, a steroid myopathy should be to distinguished from an exacerbation of underlying myositis [75]. Flare-up of myositis is associated with increasing serum creatine kinase and fibrillation potentials on EMG whereas the rare steroid myopathy is not.

CONCLUSION

A plethora of drugs have the potential to cause muscle damage including the commonly prescribed statin drugs. A good medical history including current and previous medication history should be obtained to correlate the time profile of exposure to onset of neuromuscular deficit. In direct myotoxicity, stopping the offending agent is critically important as it leads to muscle cell regeneration and onset of improvement of muscle symptoms within two months. However, immune-mediated myopathies such as SANAM progress beyond that timeframe and are associated with significant morbidity and mortality if left untreated. SANAM requires chronic treatment with multiple long-term immunosuppressive agents. It is also important to distinguish SANAM from rhabdomyolysis in the acute setting as management of these two conditions is quite different. Clues favoring SANAM over rhabdomyolysis are the degree of creatine kinase elevation, EMG evidence of pseudomyotonia, HMGCR antibody status and histopathologic evidence of MHC-I expression on the surface of myofibers.

In addition to statins, immune checkpoint inhibitors are novel and powerful, increasingly used anticancer agents that enhance the immune response. These agents pause significant challenges in some patients, but there is a special concern about worsening any underlying neuromuscular disorders, particularly, in patients with preexisting immune-mediated muscle disease or other autoimmune disorders. In these challenging cases, multidisciplinary care and discussion of risks, benefits and alternatives to immune checkpoint inhibition in the treatment of advanced cancer between the treating oncologist, the neurologist/neuromuscular specialist, cardiologist, the rheumatologist and the patient are extremely important. Careful mutlidisciplinary monitoring of cancer patients treated with these life-saving therapies will promote prompt and appropriate management to mitigate these increasingly recognized adverse drug reactions.

Acknowledgements

None.

Financial support and sponsorship

The present work was supported by a CTSA grant from NCATS awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research (# UL1TR000001). The contents are solely the responsibility of the authors

and do not necessarily represent the official views of the NIH or NCATS.

Conflicts of interest

There are no conflicts of interest.

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