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Statin-induced myalgia and myositis: an update on pathogenesis and clinical recommendations

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Abstract

Introduction—Musculoskeletal manifestations are well-recognized side effects of treatment with statins. New advances in this field have appeared in recent years. This review focuses on the diagnosis of these conditions and their underlying pathogenesis, in particular immune-mediated necrotizing myopathy.

Areas covered—Clinical phenotypes including rhabdomyolysis, myalgia and/or mild hyperCKemia, self-limited toxin statin myopathy, and immune-mediated necrotizing myopathy are herein described. Therapeutic recommendations and a diagnostic algorithm in statin-associated myopathy are also proposed. The etiology and pathogenesis of statin-induced myopathy has mainly focused on the anti-HMGCR antibodies and the responsibility of the immune-mediated necrotizing myopathy is discussed. The fact that patients who have not been exposed to statins may develop statin-associated autoimmune myopathy with anti-HMGCR antibodies is also addressed. The literature search strategy included terms identified by searches of PubMed between

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Declaration of interest

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1969 and December 2017. The search terms 'myositis', 'statin-induced autoimmune myopathy', 'immunemediate necrotizing myopathy', 'statins', 'muscular manifestations', and 'anti-HMGCR antibodies' were used.

Expert commentary—Full characterization of the known phenotypes of statin toxicity and the specific role of the anti-HMGCR in those exposed and not exposed (i.e. juvenile forms) to statins and in some types of neoplasms is of paramount relevance.

Keywords

Myositis; statin-induced autoimmune myopathy; immune-mediate necrotizing myopathy; statins; muscular manifestations; anti-HMGCR antibodies

1. Introduction

Drugs that inhibit the enzyme, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), known as statins, are one of the most widely used medications [1]. Statin use is associated with reductions in cardiovascular risk and mortality due to cardiovascular disease [2,3]. However, a well-recognized adverse effect of these drugs is muscle toxicity. Although data from randomized clinical trials suggest that this would not be a significant reason for discontinuing these drugs, patients may show poor adherence to statin regimens because of myalgia and other muscle complaints [4,5].

Currently there is no consensus regarding the terminology physicians should use for the muscle involvement occurring in patients receiving statins. Hence, *myalgia*, *myositis*, and *myopathy* are used interchangeably, and this adds some confusion to the topic [6–8]. There is some epidemiological evidence that adverse effects of statins on muscle are more common in patients with predisposing factors, such as a history of increased creatine kinase (CK) levels, a family history of myopathy, or a previous diagnosis of neuromuscular diseases or hypothyroidism [8]. Moreover, certain genetic factors may increase the risk of experiencing statin-induced muscle toxicity. One of these is a common single-nucleotide polymorphism in the *SLCO1B1* gene, which is associated with a higher risk of myopathy in patients taking simvastatin, although it is uncertain whether the risk also applies to other statins (e.g. rosuvastatin or atorvastatin) [9].

Several scoring systems have been designed to quantitate the risk of developing statin-associated muscle symptoms and to manage goal-inhibiting statin intolerance [6,10], but in clinical practice, it seems reasonable to work with four separate clinical scenarios that have different diagnostic or treatment implications: rhabdomyolysis, myalgia and mild hyperCKemia, self-limited toxic statin myopathy, and the recently described immune-mediated necrotizing myopathy. This review describes these conditions, the challenges of their diagnosis, and their pathogenesis, with a particular focus on immune-mediated necrotizing myopathy. Recommendations for clinicians and suggested approaches for managing these patients are discussed.

2. Defining clinical phenotypes

From the clinical viewpoint, patients with statin-associated myopathy can be divided into four groups [11,12]: those with rhabdomyolysis, those with myalgia or mild hyperCKemia (<5.0 times the upper limit of normal), those having self-limited toxic statin myopathy, and those with myositis (i.e. the recently described immune-mediated necrotizing myopathy with anti-HMGCR antibodies).

2.1. Rhabdomyolysis

Rhabdomyolysis, the most severe form of acute muscle disease associated with statins, is fortunately, very rare, affecting less than 1 patient per 100,000 treated per year with these drugs [13]. High CK concentrations (>100 -fold the upper limit of normality) are characteristic of rhabdomyolysis, but what defines the syndrome is evidence of myoglobinuria and renal impairment, due to acute tubular necrosis caused by myoglobin precipitation in the renal tubules [14]. Rhabdomyolysis is a life-threatening condition; statins must be discontinued and in most cases, avoided in the future for safety reasons. Dark urine with a positive dipstick test may be mistaken for hematuria. The absence of red cells in the urine sediment supports the diagnosis of myoglobinuria. In severe cases of rhabdomyolysis, muscle weakness may be a cardinal manifestation, but it is usually transitory, disappearing a few days after stopping the drug. Muscle biopsy is not generally indicated, and when it is necessary for diagnostic purposes, it should be performed several weeks or months after the clinical event.

2.2. Myalgia and/or mild hyperCKemia

This mild form of statin-induced muscle toxicity is often seen in clinical practice. Myalgia or muscle pain is the most common symptom and a frequent cause of statin discontinuation. However, in a Cochrane Foundation analysis of 37,939 patients receiving statins in 9 clinical trials [15], only 9.4% (3551 patients) developed symptoms of myalgia, a rate similar to that found in patients receiving a placebo. It has been argued that these studies may be biased, as patients who had developed some type of muscle disease in the past were excluded. Supporting this concept, the prevalence of myalgia in observational studies is higher, close to 20% [8,16–18]. On the other hand, clinicians have to take into account the nocebo effect, meaning the negative expectations of the patient and their doctors regarding muscular manifestations attributed to statins. This nocebo effect may partially explain the muscle aching in absence of biochemical substrate that is detected in observational studies and not in randomized double-blind placebo-controlled trials [19].

Clinically, the pain experienced is usually in the calves and thighs, but it is sometimes diffuse, affecting all muscles. Although myalgia is a cause of statin discontinuation, it is not a life-threatening situation. It can be accompanied by a mild CK elevation, usually reaching less than 1000 IU/L (<5 -fold the upper limit of normal), which in itself, is not a mandatory reason for discontinuing statin treatment. Moreover, the outcome of this clinical syndrome is highly variable; it can improve or not after withdrawing the offending drug. Some patients continue experiencing myalgia and/or mild CK elevations even after statins have been stopped, and others improve despite continuation of the drug [20,21].

2.3. Self-limited toxic statin myopathy

Some patients develop toxic myopathy during treatment with statins, a condition that is not immune-mediated. The severity of the presentation varies, with proximal muscle weakness preventing the basic activities of daily living in more severe forms and high CK levels, usually between 10 and 100 times the upper limit of normality (2000–20,000 IU/L). Myalgia is also a common symptom.

Muscle biopsy is usually performed in these patients, although it can be deferred for 4–6 weeks after statin discontinuation while monitoring the patients' clinical evolution. If the clinical complaints progressively improve, muscle biopsy is not necessary. Pathological study shows necrosis and regenerating muscle fibers, but none of the other characteristic immune-mediated features. Nevertheless, it is well-recognized that regenerating muscle fibers can express major histocompatibility complex (MHC) class I, and this may make it difficult to establish whether the pathological findings indicate an immune-mediated phenomenon. Determination of antibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR antibodies) [22] is essential to confirm an immune-mediated condition and promptly start immunosuppressive therapy, as patients with self-limited statin toxic myopathy generally test negative to these antibodies [23].

2.4. Immune-mediated necrotizing myopathy and anti-HMGCR antibodies

The last of the four muscle conditions associated with statin treatment, immune-mediated necrotizing myopathy (IMNM), should be considered a true autoimmune myopathy. Affected patients show progressive proximal muscle weakness involving both limb girdles, CK values between 10 and 100 times the upper limit (2000 and 20,000 IU/L), myopathic electromyography findings, and muscle biopsy usually showing necrosis with regeneration of muscle fibers and scarce inflammation, mainly composed of macrophages [24,25]. Certain immune-mediated features, such as endothelial membrane attack complex (MAC) deposition in non-necrotic fibers and MHC class I expression are additional pathologic features of this condition (Figure 1). One differential characteristic is that statin withdrawal does not usually improve the patient's symptoms. Immunosuppressive treatment is required to obtain a clinical response.

IMNM was first described by a group of researchers from the Johns Hopkins Myositis Center in Baltimore. The clinical picture was associated with a new autoantibody against a protein doublet of 100–200 kDa detected by immunoprecipitation techniques [24]. Later, the same group identified the protein, HMGCR, as the rate-limiting enzyme in cholesterol synthesis [26]. This form of autoimmune myopathy is now recognized worldwide, with authors from several countries, from Asia to Europe and from the United States to New Zealand, reporting their experience [27–32].

This autoimmune myopathy is rare, with an estimated incidence of 2–3 new cases in every 100,000 patients exposed to statins [33]. In addition, it is associated with a specific immunogenetic background, in which adults often show the human leukocyte antigen (HLA) DRB1*11:01 and children DRB1*07:01 [34,35]. Most patients from the population exposed to statins, and even those with familial hypercholesterolemia receiving high doses of the

drug do not develop this clinical picture, and test negative to anti-HMGCR antibodies when screened [36].

Over the years, new and more efficient techniques to detect anti-HMGCR autoantibodies have been developed to replace the expensive and time-consuming immunoprecipitation method [37]. Commercial ELISA or blot tests are easy to perform and work acceptably well. A complementary and even less expensive test to screen for these antibodies is the detection of a characteristic HALIP (**H**MGCR-**A**ssociated **L**iver **I**ndirect immunofluorescence **P**attern), using cryostat triple tissue sections (rat liver, kidney, and stomach), which is subsequently confirmed by ELISA or blotting (Figure 2) [28]. Although immunoprecipitation remains the gold standard technique for detecting anti-HMGCR antibodies, it is now used only for confirmation purposes in rare cases with inconclusive results on other tests.

IMNM has a heterogeneous clinical picture with widely varying degrees of muscle involvement. Occasionally patients may improve after statin withdrawal, but usually they require immunosuppressive treatment. The standard therapy includes various immunosuppressants. Azathioprine and methotrexate are the most common, but other drugs such as calcineurin antagonists (cyclosporine or tacrolimus) and mycophenolate mofetil are being used increasingly more often. A recent study has reported that intravenous immunoglobulin, the only agent with proven effectiveness for treating inflammatory myopathies in a randomized controlled clinical trial [38], seems to be the best option for treating statin-associated immune-mediated necrotizing myopathy [33,39].

Clinicians sometimes encounter patients with aggressive forms of the disease (Figure 3), in which glucocorticoids, intravenous immunoglobulins, and a single immunosuppressive drug do not suffice to improve the condition. In this situation, other drugs such as rituximab or even plasmapheresis may be required for treatment. Patients who do not respond well to conventional therapy may develop extremely severe muscle manifestations, which can include severe dysphagia requiring nasogastric tube feeding and dyspnea resulting from diaphragmatic muscle involvement that can lead to respiratory failure.

In muscle biopsy specimens of patients with anti-HMGCR-induced myopathy, the pathological findings predominantly show necrosis with scarce inflammatory infiltrate, as in other immune-mediated necrotizing myopathies. However, in some rare cases, there is a pathological picture of marked inflammation [29,31,40–43]. Furthermore, an unknown myopathy of genetic or metabolic origin is seen in some muscle biopsy analyses of patients with suspected statin-related myopathy, suggesting that the drug may act as a 'trigger' for the condition (unpublished personal observations).

There is a well-known association between cancer and some types of idiopathic inflammatory myositis, including immune-mediated necrotizing myopathy. In some studies, the presence of anti-HMGCR autoantibodies was marginally associated with a higher risk of developing cancer, although the risk was lower than in patients with autoantibody-negative immune-mediated necrotizing myopathy [44]. The risk doubles with anti-HMGCR antibodies, but in seronegative patients, it is more than eightfold higher than in the general

population. Although studies in Japan seem to confirm the association between cancer and anti-HMGCR [45], it is not supported in all publications [31,46].

In the original report describing anti-HMGCR antibodies, most, but not all patients with anti-HMGCR-associated myopathy had been exposed to statins (72.7% of the total) [24]. The percentage of unexposed patients is even higher in other series, such as the largest cohort of European patients, in which 45.6% of patients with anti-HMGCR-associated myopathy were statin-naïve [32]. Furthermore, in recent reports including children with inflammatory myopathy, some of them misdiagnosed as having dystrophy, none of the children had received statins [34,47,48]. Therefore, a relevant question remains: Is the clinical management of anti-HMGCR-associated myopathy the same in patients who have been exposed to statins and those who have not?

3. Etiology and pathogenesis

Statin-induced myopathy encompasses a heterogeneous group of muscle manifestations that have not yet been well characterized. Mitochondrial dysfunction, oxidative stress, and several mechanisms derived from impaired mevalonate metabolism, such as isoprenylation of small G-proteins, have been implicated in the mechanism of statin toxicity [49–51].

Genetic susceptibility related to the pharmacokinetics and pharmacodynamics of the drug is also of paramount relevance in statin-related myopathy. Polymorphisms of the *SLCO1B1* gene are the best-known pharmacokinetic-related alteration, although polymorphisms of other genes have also been described [9]. Regarding pharmacodynamics, certain genetic factors can increase the risk of statin-induced myopathy. Some examples are those associated with plasma membrane calcium transporting ATPase or with mitochondrial energy production regulated by the CoQ2 gene. This gene codes for the coenzyme Q10, known as ubiquinone, which is located in the phospholipid bilayer of mitochondria and is essential for obtaining energy, especially in muscle tissue [8,52].

Recently, a new etiopathogenetic mechanism has been proposed, in which the immune system also plays a role. This is the case of immune-mediated necrotizing myopathy and antibodies against HMGCR, the enzyme that is usually upregulated by statins. Statins upregulate HMGCR and overexpression of this enzyme likely facilitates presentation of highly immunogenic HMGCR peptides by the HLA DRB1*11:01, thus triggering the autoimmune disease [35,53].

In other words, a new paradigm of disease mechanism is elicited. In susceptible patients who have a characteristic HLA or an appropriate genetic background, HMGCR, the molecular target of statins, may trigger the autoimmune phenomenon after some type of interaction with the drug. Once the autoimmune process is started, HMGCR overexpression by statins is not needed to maintain the disease, as regenerating cells naturally express HMGCR [54,55] and will maintain the feed-forward loop of autoimmunity. This pathogenetic model is shown in Figure 4. Anti-HMGCR can be found in muscle cells, and some authors have reported that levels of this antibody correlate with the CK concentration and clinical disease activity, thus suggesting a possible role of these antibodies in the pathogenesis of the disease [26,56].

In addition, experimental studies in muscle biopsies of patients with anti-HMGCR have shown that these autoantibodies may impair muscle regeneration and induce muscle atrophy [57].

A challenging scenario is one in which patients who have not been exposed to statins show a full-blown clinical syndrome of immune-mediated necrotizing myopathy and anti-HMGCR antibodies. These patients are usually younger and more difficult to treat [46]. Some authors have proposed that consumption of red yeast rice, *Puerh* tea, or food containing certain types of oyster mushrooms, all natural sources of statins, may explain this association. *Monascus purpureus*, a mold traditionally used in East Asia to dye and conserve food, participates in the fermentation of red yeast rice, and gives it the characteristic red color. This mold produces lovastatin in its natural form, the so-called monacolin K, its pharmacologic active compound, and a well-known type of statin [58]. After long-term storage, *Pu-erh tea* is rich in *Aspergillus terreus*, which plays a role in its maturation and specific flavor and is also a source of lovastatin [59]. Of note, the first statin synthesized in 1976 by Akira Endo, a Japanese biochemist, was derived from the fungus species *Penicillium citrinum* [60]. Hence, it is reasonable to suggest that statin-naïve patients with anti-HMGCR-associated myositis have somehow been inadvertently exposed to natural sources of statins. The fact that Asian cohorts, where the diet is rich in statin-containing food, show a higher prevalence of statin-naïve anti-HMGCR patients [29,30] also supports this theory, although this could be due in part to the pharmacokinetics differences observed in distinct ethnicities. Epidemiologic studies focused on clarifying this issue would undoubtedly be of great interest.

Also of interest, an indirect immunofluorescence study reported that the characteristic HMGCR-associated immunofluorescence pattern, HALIP, was recognized in rat liver tissue and confirmed by immunoabsorption with human purified HMGCR antigen [28]. This finding prompted us to speculate that the same mechanism of toxicity and immunity could also be the cause of autoimmune hepatitis associated with statin-induced liver toxicity, a rare but well-described condition. This disorder occasionally courses as a self-sustained autoimmune hepatitis that persists even after statins have been stopped, in the same manner as immune-mediated necrotizing myopathy [61–64]. However, on analysis of 30 patients with autoimmune hepatitis and 30 others with primary biliary cholangitis in our center, as well as 1 patient with autoimmune hepatitis showing a tight temporal relationship with initiation of statins (personal observation), anti-HMGCR antibodies tested negative in all cases. To the best of our knowledge only one such a case, which combine IMNM and autoimmune hepatitis, positive to anti-HMGCR, has been published until now [65].

4. Clinical recommendations

A practical approach to establish clinical recommendations regarding the muscle complaints related to statin use takes into account which of the abovementioned phenotypes best fits a given patient. Nevertheless, as a set of general rules, it is recommended to first review the indication for statin use in terms of cardiovascular risk, exclude secondary causes of myopathy such as hypothyroidism or the presence of any well-defined myopathy (e.g. McArdle disease or Steinert myotonic dystrophy), and explore whether a high level of physical activity was related with the patient's signs and symptoms.

In a patient with myalgia, serumCK below 1000 IU/L (<5 times the upper limit of normal), and no muscle weakness on physical examination, it is probably safe to maintain the drug and monitor CK levels, which should be stable or have normalized at the next follow-up visit. If CK values rise to more than 10 times the upper limit, the clinician should assess the risk/benefits of drug withdrawal, although it is probably warranted. As a general rule, in a high-risk patient (e.g. previous myocardial infarction) who has myalgia with normal serum CK values and no muscle weakness, we do not recommend withdrawing statin treatment.

When statin administration is associated with rhabdomyolysis, a severe condition, the advice is clear: withdraw the statin and do not administer it in the future. If such as patient is at high cardiovascular risk, we suggest the use of other, recently approved effective drugs, such as PCSK9 inhibitors [66]. These monoclonal antibodies (e.g. evolocumab, alirocumab, and bococizumab), which act against the proprotein convertase, have proven effective in reducing cardiovascular events and could be an alternative to statin therapy in severe cases of drug toxicity, such as rhabdomyolysis.

It is more difficult to establish clinical recommendations in the other two phenotypes: self-limited toxic myopathy and statin-induced autoimmune myopathy. In the first case, drug withdrawal usually suffices. Muscle biopsy can sometimes be misleading in these patients, and it is important to test for anti-HMGCR autoantibodies to differentiate between the two conditions. If the patient does not improve within 2 weeks after discontinuing the drug and anti-HMGCR antibodies test positive, the diagnosis of immune-mediated necrotizing myopathy is supported and immunosuppressive therapy should be considered. If such a patient is at high cardiovascular risk, clinicians may try to rechallenge the drug, using another statin, a lower dose, or an every-other-day schedule, with strict monitoring of the patient's CK levels and muscle strength. PCSK9 inhibitors may be an alternative option, as their mechanism of action is radically different from that of statins, but there is no experience yet in this clinical scenario. Most of the related recommendations are included in Table 1 and the diagnostic algorithm (Figure 5).

No guidelines are available for the management of statin-induced muscle disorders. The recommendations reported here are based on our personal experience and are fundamentally in accordance with guidelines on statin use endorsed by scientific societies or working groups [6,8].

5. Expert commentary

Statin-induced muscle disorders are not rare. It is important to fully characterize the known phenotypes of statin toxicity as well as any new ones that may appear to delineate proper management of each type.

Several questions that are now unanswered will be resolved over the next few years. Epidemiologic studies investigating the role of other sources of statins in patients with anti-HMGCR associated myopathy who have not been exposed to medical statins will help to elucidate the pathophysiologic mechanisms causing this condition. Research will also be done in juvenile and pediatric forms of anti-HMGCR myopathy for this same purpose. The

hypothetical relationship with cancer and the appropriate genetic background that contributes to explain why some patients and not others develop the syndrome will be clarified in the near future, perhaps with genome-wide association studies, next-generation sequencing studies, or even epigenetic studies.

Data on the novel toxic-immune disease-causing mechanism will contribute to our understanding of statin-induced muscle disorders and may be applicable to other clinical phenomena and diseases, such as a drug-related liver toxicity and autoimmune hepatitis, and other immune-mediated diseases in which the trigger can be a drug or toxic agent.

Therapeutic guidelines based on evidence-based medicine are lacking for this condition. Randomized, controlled clinical trials are needed to establish appropriate recommendations. Given the rarity of some of these diseases, international initiatives are advocated to join efforts. In the interim, observational studies reporting the experience with different therapeutic strategies are also endorsed.

We should remember that new drugs such as PCSK9 inhibitors have shown great potential in the treatment of high LDL-cholesterol levels and may be a good option for reducing cardiovascular events in patients formerly receiving statins. Time will tell whether statins can be easily substituted by these drugs, and whether both types of treatment can be safely used together to improve the prognosis of patients at high cardiovascular risk.

6. Five-year view

Over the next 5 years, research will help to unravel the epidemiology and the mechanisms that underline those patients with statin-induced autoimmune myopathies not apparently exposed to statins, and the case of children with autoimmune myopathy with anti-HMGCR antibodies. Analysis of the feasibility of different serological test or provocation test to ascertain the role of *Aspergillum sp.* or others yeast that could be involved in these disease may be useful ways to address this issue. Whether these autoantibodies are pathogenic or not will be established over the next years. The new paradigm that considers the disease as the conjoint of toxicity and autoimmunity could be applied to other autoimmune disorders.

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Key issues

- Patients with autoimmune myopathy associated with statin use and anti-HMGCR antibodies show a pathological picture on muscle biopsy that fits with immune-mediated necrotizing myopathy. Occasionally, a typical inflammatory infiltrate can also be seen. The term *statin-induced autoimmune myopathy* encompasses this clinical spectrum.
- Statin-naïve patients with anti-HMGCR antibodies and autoimmune myopathy have been described, including children. Other sources of possible statin exposure produced by *Aspergillus* spp., *Penicillium* spp., and other molds should be investigated.
- The clinical presentation of *statin-induced autoimmune myopathy* is heterogeneous. There are mild forms that do not need immunosuppressants and severe forms that are refractory to intense immunosuppression. Clinicians should be aware of this heterogeneity.
- Intravenous immunoglobulin seems to be the best treatment for patients diagnosed with immune-mediated necrotizing myopathy and anti-HMGCR antibodies, and should be included in all therapeutic schemes.
- Immune-mediated conditions such as statin-associated myopathy establish a new paradigm in which drug-related muscle toxicity may modify the HMGCR molecule and trigger an autonomous, autoimmune phenomenon.

Figure 1. Immune-mediated necrotizing myopathy. Necrotic muscle fiber cells (arrows). (a) Hematoxylin-eosin, (b) Numerous regenerating fibers are seen (arrows). Masson Trichrome. (c) Universal sarcolemmal MHC class I positive (stronger in regenerating cells). (d) MHC class I negative control (positivity only in endothelial cells). All samples are frozen tissue. Published with permission of Elsevier. Original source: Alvarado Cárdenas et al. *Med Clin (Barc)* [63]. Copyright © 2015 Elsevier España, S.L.U. All rights reserved.

Figure 2.
HALIP indirect immunofluorescence pattern on rat liver cryostat section. Confocal microscope FV (Olympus $\times 200$)²⁷.

Figure 3.

Clinical, functional, and biological evolution of a severe form of IMNM (see description in the text). GC: glucocorticoids, IVIG: intravenous immunoglobulin, MMT: manual muscle test, NGT: nasogastric tube, PMF: plasmapheresis, RTX: rituximab.

Figure 4.
Etiopathogenesis of statin-induced immune-mediated necrotizing myopathy. EXPERT
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Figure 5.

Diagnostic algorithm in statin-associated myopathy. CK: creatine kinase (values are intended to be approximate); EMG: electromyography; HMGCR: 3-hydroxy-3-methylglutaryl coenzyme A reductase; IMNM: immune-mediated necrotizing myopathy. Dotted line indicates that muscle biopsy is not always mandatory (see text).

Table 1

A comparison of different statin-induced muscle manifestations.

	Myalgia and/or mild elevated CK	Self-limited toxic myopathy	IMNM	Rhabdomyolysis
Symptoms	Myalgia (++) Muscle weakness (–)	Proximal muscle weakness (++) Myalgia (+)	Proximal muscle weakness (+++) Myalgia (++) Dysphagia (+/++) Ventilatory failure (+/–)	Myoglobinuria Renal failure Muscle weakness (++) Myalgia (++)
Maximum CK (IU/L)	<5 × UNL [<1000 IU/L]	<100 × UNL [<20,000 IU/L]	>10 < 100 × UNL [>2000 < 20,000 IU/L]	>100 × UNL [>20,000 IU/L]
Muscle biopsy	Not mandatory ^a	Myofiber necrosis with no immune findings	Myofiber necrosis MHC class I upregulation MAC deposition on non-necrotic fibers	Massive necrosis ^b
Genetic Background		SNP in <i>SLCO1B1</i> gene	HLA-DRB1*11:01	SNP in <i>SLCO1B1</i> gene
Anti-HMGCR antibody	Negative	Negative	Positive	Negative
Clinical course after withdrawal	Unpredictable (but good outcome)	Improvement spontaneously	Persistent/progressive weakness	Total recovery ^c
Recommended therapy	None	Statin withdrawal (or dose reduction)	Statin withdrawal Immunosuppression	Support and avoid statins in the future

^aMinimal changes include cytochrome oxidase (COX) negative fibers, vacuolization, and type 2 fiber atrophy, which are nonspecific findings.

^bFor diagnostic purposes, muscle biopsy should be performed several weeks or months after the clinical event.

^cDamage could remain.

IMNM: immune-mediated necrotizing myopathy; MAC: membrane attack complex; MHC: major histocompatibility complex; SNP: single-nucleotide polymorphism (for simvastatin); UNL: upper normal limit.