



EDUCATIONAL OBJECTIVE: Readers will recognize autoimmune necrotizing myopathy if it occurs in their patients taking statins

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Identifying statin-associated autoimmune necrotizing myopathy

ABSTRACT

Statins up-regulate expression of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis and the major target of autoantibodies in statin-associated immune-mediated necrotizing myopathy. As muscle cells regenerate, they express high levels of HMGCR, which may sustain the immune response even after statin therapy is stopped. Awareness of this entity will help physicians who prescribe statins to take action to limit the associated morbidity.

KEY POINTS

Most cases of muscle symptoms associated with statin use are a direct effect of the statin on the muscle and resolve after the statin is discontinued.

In contrast to simple myalgia or myositis, statin-associated autoimmune necrotizing myopathy can persist or even arise de novo after the statin is stopped.

This condition presents with symmetric proximal arm and leg weakness and striking elevations of muscle enzymes such as creatine kinase.

Treatment can be challenging and requires immunosuppressive drugs; referral to a specialist is recommended.

Statin therapy should be discontinued once this condition is suspected. Patients who continue to have elevated muscle enzymes or weakness should undergo further testing with electromyography, magnetic resonance imaging, and muscle biopsy.

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STATINS ARE AMONG THE MOST widely prescribed drugs, as they reduce cardiovascular risk very effectively. They work by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), a key enzyme in cholesterol biosynthesis. Although most patients tolerate statins well, muscle-related toxicity can limit the use of these drugs.

Recently, progressive necrotizing myopathy leading to profound weakness has been directly linked to statin therapy. Proper recognition of this ominous complication is important to prevent further damage from statin use.

■ STATIN-ASSOCIATED MUSCLE EFFECTS: A SPECTRUM

Muscle symptoms are among the best known and most important side effects of statins, ranging from asymptomatic, mild elevation of creatine kinase and benign myalgias to life-threatening rhabdomyolysis. As the various terms are often used inconsistently in the literature, we will briefly review each entity to put immune-necrotizing myopathy in its proper context on the spectrum of statin-associated muscle symptoms.

Myalgia

Myalgia, ie, muscle pain without elevation of muscle enzymes, is the most common side effect of statins. The incidence is about 10% in observational studies^{1,2}; however, the incidence in the real world of clinical practice seems much higher. Myalgias can present as widespread pain or as localized pain, usually in the lower extremities. Muscle cramps and tenosynovitis-related pain are commonly reported.

Several clinical predictors of increased risk of statin-associated muscle pain were noted in

the Prediction of Muscular Risk in Observational Conditions (PRIMO) study,² assessing mild to moderate muscular symptoms in patients on high-dose statins. These included a history of muscle pain with another lipid-lowering agent, a history of cramps, a history of elevated creatine kinase levels, a personal or family history of muscle symptoms, untreated hypothyroidism, and a background of fibromyalgia-like symptoms. The incidence of muscle symptoms increased with the level of physical activity, and the median time of symptom onset was 1 month after starting statin therapy or titrating to a high dose.

In patients with myalgia alone, symptoms often improve when the statin is stopped.

Myopathy, myositis

The general terms *myopathy* and *myositis* have been used to refer to elevated muscle enzymes together with the muscle symptoms of pain, cramps, soreness, or weakness. An analysis of 21 clinical trials of statin therapy found that myopathy (creatinine kinase level more than 10 times the upper limit of normal) occurred in 5 patients per 100,000 person-years.³ The incidence of myopathy increases when statins are used in high doses.

In another cohort of patients seen for statin intolerance,¹ conventional risk factors for overt myositis included renal disease, diabetes, and thyroid disease. Electrolyte abnormalities did not differ between statin-tolerant and statin-intolerant patients.¹

The search for genetic indicators of risk

In 2008, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group conducted a genome-wide association study to identify genetic variants associated with myopathy with high-dose statin therapy.⁴ Eighty-five patients who had developed definite myopathy (muscle symptoms with enzyme levels more than 10 times the upper limit of normal) or incipient myopathy (asymptomatic or symptomatic, but enzyme levels at least three times the upper limit of normal) while taking simvastatin 80 mg were compared with 90 controls taking the same daily dose. The study reported variants in the *SLCO1B1* gene as “strongly associated with an increased risk of statin-associated myopathy.”⁴

SLCO1B1 encodes the peptide responsible for hepatic uptake of statins, thus affecting the blood level of these drugs. Patients in the study who had the C variant, which predisposes to higher blood levels of statins, were at higher risk of myopathy than those with the T variant. The odds ratio for myopathy increased from 4.4 in heterozygotes for the C allele to 17.4 for homozygotes. This effect was similar even with lower doses of statins.⁴

We believe that these findings provide a strong basis for genetic testing of patients who may be at risk of statin-associated myopathy.

Rechallenging with a different statin

Often, patients with myopathy can be rechallenged with a different statin agent. In a study done in a lipid clinic, patients identified as having simvastatin-associated myopathy were given another statin.⁵ Between 15% and 42% tolerated the second statin, with no statistically significant difference between the tolerability rates with the different agents used (atorvastatin, rosuvastatin, pravastatin, and fluvastatin).

Rhabdomyolysis

Rhabdomyolysis, the most devastating complication of statin use, is marked by a creatine kinase level more than 10 times the upper limit of normal or greater than 10,000 IU/L, resulting from acute and massive destruction of muscle fibers and release of their contents into the bloodstream.

But rhabdomyolysis is a clinical syndrome, not solely an alarming increase in muscle enzyme levels. It can include renal failure and death. The rate of occurrence is low (1/100,000), but it can occur at any point in treatment.⁶ An analysis of Canadian and US case reports of statin-associated rhabdomyolysis showed an average of 824 cases each year.⁷ A dose-response relationship was observed with higher statin doses.

But statin-associated myopathy may not stop when the drug is stopped

The types of muscle toxicity discussed above stem from direct myotoxic effects of statins and are thought to be related to the blood concentration of the statin.^{6,8} They may be limited by genetic susceptibility. Mechanisms may include a change in muscle membrane ex-

Most patients tolerate statins well, but muscle toxicity can limit the use of these drugs

citability caused by modulation in membrane cholesterol levels, impaired mitochondrial function and calcium signaling, induction of apoptosis, and increased lipid peroxidation. Stopping the offending drug can often halt these downstream effects—hence the dictum that statin myopathy is self-limiting and should resolve with cessation of the drug.

But as we discuss in the following sections, some patients on statin therapy develop an immune-mediated myopathy that does not resolve with discontinuation of the statin and that may only resolve with immunosuppressive therapy.

■ STATINS AND AUTOIMMUNE NECROTIZING MYOPATHY

At the Johns Hopkins Myositis Center, a group of patients was identified who had necrotizing myopathy on biopsy but no known underlying condition or associated autoantibodies. In an attempt to establish an autoimmune basis for their disease, the sera from 26 patients were screened for novel antibodies.⁹ Sera from 16 of the patients immunoprecipitated a pair of proteins (sizes 100 kd and 200 kd), indicating these patients had an antibody to these proteins. This finding was highly specific for necrotizing myopathy when compared with controls, ie, other patients with myositis. Patients who had this finding displayed proximal muscle weakness, elevated muscle enzyme levels, and myopathic findings on electromyography; 63% had been exposed to statins before the onset of weakness, and when only patients over age 50 were included, the number rose to 83%.

This association of statins with necrotizing myopathy had been previously noted by two other groups. Needham et al¹⁰ described eight patients who, while on statins, developed myopathy that continued to worsen despite cessation of the drugs. An analysis of their muscle pathology revealed myofiber necrosis with little inflammatory infiltrate, as well as widespread up-regulation of expression of major histocompatibility complex class 1. These patients required immunosuppressive treatment (prednisone and methotrexate) to control their disease.

Grable-Esposito et al¹¹ corroborated this

finding by identifying 25 additional patients who developed a similar necrotizing myopathy while on statins.¹¹ They also noted a significantly higher frequency of statin use in patients with necrotizing myopathy than in age-matched controls with polymyositis or inclusion-body myositis.

The researchers at the Johns Hopkins Myositis Center noted the similarity between these two patient groups and their own group of patients with necrotizing myopathy. Thus, a follow-up study was done to identify the 100-kd and 200-kd autoantigens observed in their earlier study. Exposure to a statin was found to up-regulate the expression of the two molecules.¹² HMGCR was hypothesized as being the 100-kd antigen, because of its 97-kd molecular weight, and also because statin treatment had already been shown to up-regulate the expression of HMGCR.¹³ The researchers concluded that HMGCR was indeed the 100-kd antigen, with no distinctive antibodies recognizing the 200-kd protein. Although the 200-kd protein was once postulated to be a dimer of the 100-kd protein, its identity remains unknown.

The anti-HMGCR antibody was then screened for in a cohort of 750 myositis patients. The 16 patients previously found to have anti-200/100 were all positive for anti-HMGCR antibody. An additional 45 patients from the cohort (6%) were anti-HMGCR-positive by enzyme-linked immunosorbent assay, and all had necrotizing myopathy. Patients with other types of myopathy, including inflammatory myopathy, do not possess this antibody.¹²

The HMGCR antibody was quite specific for immune-mediated necrotizing myopathy, and this suggested that statins were capable of triggering an immune-mediated myopathy that is then perpetuated even if the drug is discontinued. As it was also demonstrated that statins increase the expression of HMGCR in muscle as well as in regenerating cells, the process may be sustained through persistently increased HMGCR expression associated with muscle repair.¹²

The C allele of the *SLCO1B1* gene, which has been associated with statin-associated myopathy, was not increased in this population of patients positive for anti-HMGCR. Follow-

The C variant of *SLCO1B1* increases the risk of myopathy with statins

TABLE 1

Presentation of statin-associated autoimmune necrotizing myopathy

Duration of statin use	From 2 months to 10 years ¹⁰
Muscle symptoms	Symmetric proximal arm and leg weakness, distal weakness possible, myalgia ¹¹
Other symptoms	Dysphagia, arthralgia, Raynaud phenomenon ¹¹
Muscle enzymes	Mean creatine kinase value 10,333 IU/L ⁹
Magnetic resonance imaging	Muscle edema, atrophy, fatty replacement, fascial edema ⁹
Electromyography	Irritable myopathy in most patients ¹¹
Muscle biopsy	Prominent necrotic and regenerating fibers without significant inflammatory infiltrate; diffuse or focal up-regulation of major histocompatibility complex class I expression ¹¹

up studies of the prevalence of anti-HMGCR in statin users in the Atherosclerosis Risk in Communities (ARIC) cohort, including those with self-limited statin myotoxicity, have also shown the absence of this antibody.¹⁴ This shows that anti-HMGCR is not found in the majority of statin-exposed patients and is highly specific for autoimmune myopathy. This also suggests that statin-associated autoimmune myopathy represents a pathologic process that is distinct from self-limited statin intolerance.

■ HOW THE CONDITION PRESENTS

Immune-mediated statin myopathy presents similarly to other idiopathic inflammatory myopathies such as polymyositis (TABLE 1). Symptoms often develop in a subacute to chronic course and can occur at any time with statin treatment. In one study,¹⁰ the average duration of statin use before the onset of weakness was 3 years (range 2 months to 10 years). In some patients whose statin had been stopped because of abnormal creatine kinase levels, weakness developed later, at a range of 0.5 to 20 months. Even low doses of statins (such as 10 mg of simvastatin) have been found to trigger this condition.¹⁰

Patients uniformly develop symmetric proximal arm and leg weakness, and distal weakness can also occur.¹¹ Other features have included dysphagia, arthralgias, myalgias, and Raynaud phenomenon.⁹ Men and women are

represented in roughly equal numbers.

The muscle enzymes are strikingly elevated in this disease, with a mean creatine kinase value of 10,333 IU/L at initial presentation.⁹ Although the creatine kinase level may be very elevated, patients often do not present with weakness until a certain threshold value is reached, in contrast with patients with anti-signal recognition particle necrotizing myopathy, who can present with profound weakness at a lower level. Hence, by the time patients are clinically symptomatic, the process may have been going on for some time. Despite the seemingly massive leak in muscle enzymes, the patients do not develop rhabdomyolysis. Inflammatory markers need not be elevated, and an association with other antibodies such as antinuclear antibody is not often seen.

Magnetic resonance imaging of the thigh has shown muscle edema in all patients.⁹ In decreasing order of frequency, other findings are atrophy, fatty replacement, and fascial edema.

Electromyography of involved muscle has shown irritable myopathy in most patients (88%) and nonirritable myopathy in a few.

Muscle biopsy studies have shown prominent necrotic and regenerating fibers without significant inflammatory infiltrate.¹¹ There is also myophagocytosis of necrotic fibers and diffuse or focal up-regulation of major histocompatibility complex class I expression.¹⁰

Anti-HMGCR is highly specific for statin-associated autoimmune necrotizing myopathy

■ PATIENTS WITH ANTI-HMGCR WHO HAVE AND WHO HAVE NEVER TAKEN STATINS

When the anti-HMGCR antibody was tested for in the Johns Hopkins cohort,¹² 33% of patients with a necrotizing myopathy associated with this antibody had never taken a statin. The two groups were clinically indistinguishable, save for a few aspects. Compared with patients who had taken a statin, those who had never taken a statin were younger (mean age 37 vs 59), had higher levels of creatine kinase (13,392 vs 7,881 IU/L), and had a different race distribution (46.7% vs 86.7% white). Initial HMGCR antibody levels were also noted to correlate with creatine kinase levels and strength in statin-exposed patients but not in those who had never taken a statin.¹⁵

We hypothesize that in patients who have never taken a statin, other genetic or environmental factors may be the cause of the increased HMGCR expression, which then triggers the autoimmune response. Until further data are gathered, we should probably treat these patients as we treat those who develop this disease after taking a statin, and avoid giving them statins altogether.

■ MANAGEMENT OF STATIN-ASSOCIATED AUTOIMMUNE NECROTIZING MYOPATHY

Treatment of statin-associated autoimmune necrotizing myopathy can be challenging and requires immunosuppressive drugs.

Statin therapy should be stopped once this condition is suspected. Patients who continue to have elevated muscle enzymes or weakness should undergo further testing with electromyography, magnetic resonance imaging, and muscle biopsy. Electromyography detects myopathy and shows chronicity, distribution, and degree of severity. Although not necessary for diagnosis, magnetic resonance imaging helps to evaluate the extent of muscle involvement and damage and provides guidance when choosing a site for muscle biopsy. Muscle biopsy is necessary to determine the actual pathology and to exclude mimics such as dystrophy or metabolic myopathies.

When an immune-mediated myopathy is confirmed, prompt referral to a rheumatologist or a neuromuscular specialist is recommended.

Steroids are usually the first-line treat-

ment for this disease. Other immunosuppressives, such as methotrexate, azathioprine, mycophenolate mofetil, and rituximab have been used with varying levels of success. In our experience, intravenous immunoglobulin has been particularly beneficial for refractory cases. With treatment, muscle enzyme levels and weakness improve, but relapses can occur. The ideal choice of immunosuppressive therapy and the duration of therapy are currently under investigation.

Rechallenge with another statin

At this time, the issue of rechallenging the patient with another statin has not been clarified. Given the autoimmune nature of the disease, we would avoid exposing the patient to a known trigger. However, this may be a difficult decision in patients with cardiovascular risk factors who require statins for primary or secondary prevention. We suggest using alternative cholesterol-lowering agents first and using them in combination if needed.

We have had some success in maintaining a handful of patients on a statin while treating them concurrently with immunosuppression. This is not ideal because they are constantly being exposed to the likely trigger for their disease, but it may be unavoidable if statins are deemed absolutely necessary. We have also had a patient with known statin-associated immune-mediated necrotizing myopathy who later became profoundly weak after another physician started her on a newer-generation agent, pitavastatin. This suggests to us that rechallenging patients, even with a different statin, can have deleterious effects.

■ IMPLICATIONS FOR CLINICAL PRACTICE

The true prevalence of statin-associated autoimmune myopathy in practice is unknown. In the Johns Hopkins Myositis Center cohort of patients with suspected myopathy, anti-HMGCR was found in 6% of the patients and was the second most frequent antibody found after anti-Jo1.¹²

Given the frequency of muscle-related complaints in patients on statins, we recommend obtaining baseline muscle enzyme measurements before starting statin therapy. As recommended by the National Lipid Association Statin Safety Assessment Task Force,

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the creatine kinase level should be measured when a patient develops muscular complaints, to help gauge the severity of the disease and to help decide whether to continue therapy.⁸ Random testing of the creatine kinase level in asymptomatic patients is not recommended.

At present, the diagnosis of statin-associated autoimmune necrotizing myopathy is based on a combination of findings—elevated muscle enzyme levels, muscle weakness, irritable findings on electromyography, and necrotizing myopathy on biopsy in a patient on a statin. The finding of the HMGCR antibody confirms the diagnosis. A test for this antibody is now commercially available in the United States. We suggest testing for the antibody in the following scenarios:

- A persistently elevated or rising creatine kinase, aspartate aminotransferase, alanine aminotransferase, or aldolase level after the statin is stopped; although no fixed

creatinine kinase level has been determined, a level above 1,000 U/L would be a reasonable cutoff at which to test

- Muscle symptoms (proximal or distal weakness) that persist 12 weeks after statin cessation regardless of the creatine kinase level, especially if the patient has dysphagia
- The finding of muscle irritability on electromyography or diffuse muscle edema on magnetic resonance imaging when testing for other myositis-specific antibodies is negative
- Muscle biopsy showing necrotizing myopathy with little or no inflammation.

In addition, since necrotizing myopathy is known to be associated with malignancy and since necrotizing myopathy is more common in older people, who are also more likely to be taking a statin, an age-appropriate malignancy evaluation is warranted as well. ■

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