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Statins, myalgia, and rhabdomyolysis

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ABSTRACT

Statin-associated muscle symptoms (SAMSs) vary considerably in frequency and severity, with a spectrum extending from myalgia with normal creatine kinase (CK) levels or asymptomatic hyperCKemia to potentially life-threatening rhabdomyolysis and necrotizing autoimmune myopathy. Myalgia with CK elevation is the most common presentation. Onset is usually within 1 month after statin initiation or dosage intensification, and the symptoms can be expected to resolve within a few weeks after treatment discontinuation. The mechanism of muscle injury combines statin accumulation within muscles, which varies with the type and dosage of the drug; muscle fragility; abnormalities in statin transport or liver metabolism; drug-drug interactions; and genetic susceptibility. HMG-CoA reductase inhibition in muscles by statins exerts pleiotropic effects that can affect energy metabolism, induce mitochondrial dysfunction, modify lipid oxidation, promote apoptosis and cell membrane lysis, alter muscle protein synthesis, or trigger an autoimmune process. Statins are used to treat several chronic conditions and comorbidities, including inflammatory rheumatic diseases, which are associated with an increased cardiovascular risk. When the cardiovascular risk is high or very high, statin therapy is indispensable and has a very favorable risk/benefit ratio. Otherwise, the risks should be weighed against the benefits before reinitiating statin therapy, and a different statin or lower dosage should be used. If statin therapy cannot be successfully reintroduced, other classes of lipid-lowering drugs should be considered. Severe SAMSs with major weakness and marked CK elevation should suggest the rare eventuality of necrotizing autoimmune myopathy and prompt an anti-HMGCR antibody assay and muscle biopsy to ensure that immunosuppressant therapy is started rapidly if needed.

Keywords: Statin. Muscle. Myalgia. Rhabdomyolysis. Myositis.
1. Statins in rheumatology

1.1. Indications

Hypercholesterolemia was present in 30% of adults aged 18 to 74 years in France in 2006-2007 (1). Together with obesity, diabetes, and hypertension, hypercholesterolemia is a major risk factor for atherosclerosis and other cardiovascular diseases, which are the second most common cause of death in France (2). Statins lower cholesterol levels by inhibiting the enzyme hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Statins are among the most widely prescribed medications in France, with 6.4 million treated patients in 2012, costing the statutory healthcare insurance slightly over 1 billion Euros (3). The introduction of statins in the 1990s proved a breakthrough in the management of dyslipidemia. Statins are used for the primary and secondary prevention of cardiovascular events. Statin therapy has been reported to decrease all-cause mortality by 10%, cardiovascular mortality by 15%, stroke by 19%, and coronary events by 23% (2).

The indications of statin therapy are based on LDL cholesterol targets that vary according to the level of cardiovascular risk. The first Systematic Coronary Risk Evaluation (SCORE) charts relied on age, sex, smoking history, systolic blood pressure, and total cholesterol. A recent update added HDL-cholesterol levels, which are often low in patients with rheumatoid arthritis (RA) (4). The SCORE charts have been validated in the general population of individuals younger than 65 years in France. They provide an estimate of the 10-year risk of cardiovascular death (2), which serves to categorize patients as follows: very high cardiovascular risk, SCORE ≥10% and documented cardiovascular disease; high cardiovascular risk, SCORE ≥5% and <10%; moderate cardiovascular risk, SCORE ≥1% and <5%); and low cardiovascular risk, SCORE <1%) (Table 1). For patients with chronic
inflammatory rheumatic disease, the EULAR recommends determining the SCORE value; in patients with RA, the result should be multiplied by 1.5 (5).

In France, SCORE charts have been used to redefine optimal LDL-cholesterol targets (2), as follows: very high risk, <1.8 mmol/L (0.70 g/L), high risk, <2.5 mmol/L (1 g/L); and moderate risk, < 3.4 mmol/L (1.30 g/L) (Table 1).

1.2. Mechanisms of action

The main effect of statins is to decrease serum levels of LDL-cholesterol, whose elevation is a well-documented causal factor of cardiovascular disease, with some of the most convincing evidence coming from studies of familial hypercholesterolemia and of vast genome-wide association studies (6). The LDL-cholesterol-lowering effect varies across statins and dosages, according to the ability of the drug to reach the hepatocytes and induce HMG-CoA reductase inhibition. HMG-CoA reductase is the key enzyme in the mevalonate pathway that produces total cholesterol (Figure 1). Specific reversible HMG-CoA reductase inhibition by statins decreases the amount of total cholesterol produced, chiefly by the hepatocytes, and stimulates the production of hepatic LDL receptors, thereby further lowering serum LDL-cholesterol levels.

HMG-CoA reductase also has many other effects, and its inhibition can alter skeletal-muscle energy metabolism by interacting with AMP kinase or decreasing the levels of certain mitochondrial coenzymes such as ubiquinone (coenzyme Q10), which is involved in the respiratory chain and fatty acid oxidation (7). HMG-CoA reductase also plays an indirect role in muscle-protein synthesis and degradation signaling pathways, by contributing to certain protein posttranslational modifications such as prenylation, which allows a fatty acid to combine with a cysteine residue, thereby ensuring anchoring to the cell membrane (7). Once in the bloodstream, statins are transported to the hepatocytes via organic anion transporting
(OAT) polypeptides. In the liver, statins are chiefly metabolized by cytochrome P450 to an active form, which is excreted into the bile via the transporters breast cancer resistance protein and multidrug resistance. Depending on serum statin levels and on any alterations in the transporters of hepatocyte metabolism, statins can accumulate within muscles, where they can exert toxic effects on calcium-dependent energy metabolism, mitochondrial function, protein synthesis, and membrane cholesterol (Figure 1).

2. Myalgia and rhabdomyolysis

Despite knowledge of the beneficial effects of statin therapy, the treatment adherence rate in a metaanalysis was only 54% (8). Adherence rates below 80% were associated with a 45% increase in mortality and a 15% increase in cardiovascular events. Thus, the management of dyslipidemia remains suboptimal, notably in the patients at highest risk, despite the widespread dissemination of recommendations (9). The reasons for this situation may include clinical inertia and concern about adverse effects, particularly on the muscle.

2.1. Frequency and severity

Statin-associated muscle symptoms (SAMSs) are the most commonly reported side effects. In an Internet survey done in the US in 2012, of 10 138 statin-exposed patients, 29% reported SAMSs (10). Moreover, of the 12% of patients who had to stop statin therapy permanently due to side effects, 60% stopped due to SAMSs.

A metaanalysis of 39 randomized controlled trials among the therapeutic and pivotal trials of statins showed similar SAMS frequencies in the statin and placebo groups: 15% for myalgia, 0.9% for creatine kinase (CK) elevation, and 0.2% for rhabdomyolysis (11). Neither was any between-group difference found for the proportion of patients who had to stop their treatment for any reason. Compared to the placebo patients, the patients given statins were
slightly more likely to experience transaminase elevation (1.4% vs. 1.1%, \(P<0.01\)) and those
given atorvastatin to report myalgia (5.1% vs. 1.6%, \(P=0.04\)) (11).

In observational studies, about 10% of patients reported muscle symptoms possibly
related to statin therapy (12,13). In the French PRIMO study of 7924 statin-treated patients,
the frequency of muscle symptoms varied across statins, with high-dose simvastatin
producing the highest rate (18.2% vs. 5.1% with fluvastatin). The symptoms lack specificity,
consisting of heaviness, stiffness, cramps, weakness, fatigability, tendon pain, or diffuse
aching. Onset was within the first month after treatment initiation or dosage intensification in
the vast majority of cases. The management consisted in changing the medication to a
different statin or a fibrate in 57% of cases, dosage reduction in 17% of cases, and definitive
statin discontinuation in 20% of cases.

Two randomized controlled trials specifically assessed the development of myalgia
during treatment with atorvastatin (14) and simvastatin (15). Of 420 statin-naive patients,
9.4% of those given high-dose atorvastatin for 6 months experienced myalgia, compared to
4.6% of placebo patients (\(P=0.05\)) (14). Myalgia was defined in this study as muscle pain for
at least 2 weeks that resolved within 2 weeks of atorvastatin discontinuation then recurred
within 4 weeks after rechallenge. The absolute CK elevation was greater in the atorvastatin
group (20.8±141.1 IU/L, \(P<0.0001\)), in which 40 patients had abnormally high values
compared to 29 in the placebo group (\(P=0.08\)). No cases of rhabdomyolysis were reported. At
completion of the 6-month study, the two groups showed no differences for muscle strength,
endurance, aerobic capacity, or level of physical activity. The other trial enrolled patients with
a history of SAMSs (15). After a washout period of at least 4 weeks, the patients were given
simvastatin 20 mg or a placebo in a crossover design for 8 weeks. Only 36% of patients
reported recurrent myalgia with simvastatin but not the placebo, and 29% of patients had
myalgia with the placebo but not with simvastatin (15).
The risk of rhabdomyolysis has been assessed using the French statutory health insurance database (16). Patients who started statin therapy for primary prevention in 2009 were included. Follow-up was 7 years. Of the 168 cases of rhabdomyolysis, 45% developed within the first 3 months after statin initiation. There were 10 fatal cases during the 18,407,391 person-month exposure, yielding an incidence rate of 1.10/10,000 person-years compared to 0.95/10,000 person-years in statin nonusers. Thus, the overall risk of rhabdomyolysis was not significantly affected by statin exposure. However, there was a significant risk increase (hazard ratio, 1.93; 95% confidence interval, 1.27-2.97) in males given high-dose statin therapy (rosuvastatin ≥10 mg, atorvastatin ≥20 mg, or simvastatin ≥40 mg), notably during the first 3 months. The analysis of concomitant medications showed that only proton pump inhibitors (which inhibit cytochrome CYP3A4) were associated with an increased risk of rhabdomyolysis.

Thus, the frequency and severity of SAMSs cover an extended spectrum. At the mild end are myalgia with normal CK levels and moderate CK elevation without symptoms, this last being seen in about one-third of patients. Rhabdomyolysis and necrotizing autoimmune myopathy (NAM) are at the severe end (17). An international panel of experts developed a classification system in 2014 (Table 2). Most patients with SAMSs have moderate CK elevation to values below 4 times the upper limit of normal. Whether myalgia can be ascribed to statin therapy in patients with normal CK levels is controversial. Patients may report fatigability, muscle weakness, aching, or cramps, usually in a proximal and symmetric distribution. The symptoms resolve after treatment discontinuation or dosage reduction. Except for NAM, SAMSs develop within 4-6 weeks after statin initiation or dosage intensification. They resolve within 2 weeks after treatment discontinuation, and their persistence should suggest another cause. CK elevation after strenuous physical activity may
be more common in statin users but seems to affect neither cardiorespiratory performance nor muscle strength (18).

2.2. **Mechanisms and risk factors of statin toxicity**

The muscle toxicity of statins involves both pharmacokinetic factors that promote statin accumulation within myocytes and underlying muscle fragility that increases vulnerability to toxic effects. In several studies, although not all, serum levels of statin or statin metabolites were higher in patients with SAMSs (7). Drug-drug interactions, as well as genetic and epigenetic factors, can alter the OAT polypeptides, the cytochrome P450 enzymes involved in metabolizing statins in the liver, and the transporters breast cancer resistance protein and multidrug resistance that ensure statin excretion in bile. The result of these effects is accumulation of the statin within muscle (7). Findings from muscle biopsy studies in patients with SAMSs are variable and sometimes conflicting. Some patients had structural muscle fiber abnormalities with atrophy of the type 2 fast-twitch fibers, evidence of necrosis or apoptosis, mitochondrial dysfunction, and lipid accumulation (7,19–21). These findings suggest that the pleiotropic effects of HMG-CoA reductase inhibition in muscle may modify the energy metabolism (AMP kinases, calcium-dependent activation), induce impairments in mitochondrial function and lipid oxidation by inhibiting coenzyme Q10, cause apoptosis and membrane lysis by altering membrane cholesterol, impair muscle protein synthesis via effects on signaling pathways, and/or trigger an autoimmune process within the muscle (Figure 1).

Risk factors include a small plasma volume or small muscle mass, both of which promote statin accumulation within muscle (older age, female sex, and low body mass index); a history of muscle disease in the patient or relatives; certain comorbidities (hypothyroidism, renal or hepatic dysfunction, and alcohol abuse); use of a highly-active statin or of high statin dosages; and concomitant exposure to drugs that affect the hepatic cytochromes or
transporters (inhibitors of cytochrome P450 or OATP1B1, colchicine, grapefruit juice) (Table 3).

3. Necrotizing autoimmune myopathy (NAM) with anti-HMGCR antibodies

The first cases of NAM associated with statin exposure were reported in 2007. This severe condition does not resolve after statin discontinuation and requires immunosuppressant therapy (22). In 2010, Mammen et al. in the US identified an antibody specifically associated with NAM and directed against the statin target HMG-CoA reductase (HMGCR) (23,24). In Europe in 2014, the groups led by Olivier Benveniste and Olivier Boyer validated the assay method and diagnostic performance of this newly discovered antibody in a cohort of 43 patients (25,26). In patients with unexplained inflammatory myositis, anti-HMGCR antibody assays are now performed routinely, in combination with anti-SRP antibody assays, to look for NAM (27). The anti-HMGCR antibody is highly specific for NAM. It is absent in most statin users with and without SAMSs (28) and is also rarely found in patients with other types of myositis or autoimmune disease (29). A pathogenic role for anti-HMGCR antibodies is supported by reports of a correlation linking their titers to clinical disease severity or degree of CK elevation (26,30). In vitro, anti-HMGCR antibodies impair myoblast fusion and differentiation, induce muscle fiber atrophy, increase the production of the proinflammatory cytokines IL6 and TNFα, and elevate markers of mitochondrial dysfunction or muscle proteolysis (31). NAM with anti-HMGCR antibody production should be considered in patients with severe muscle symptoms contrasting with the absence of pain. The CK level is very high, usually above 5000 IU/L. Muscle weakness in all four limbs is combined with impaired swallowing and hypoventilation (32). Females are predominantly affected (73%) and the risk of NAM increases with age. In contrast to NAM associated with anti-SRP antibodies, anti-HMGCR-positive forms can reveal a malignancy (standardized incidence
ratio, 2.79; 95% CI, 1.02–6.07) (33). Statin exposure is a feature in only 45% to 67% of cases of anti-HMGCR-positive NAM (24,26). The diagnosis relies on the detection of anti-HMGCR antibodies and on the muscle biopsy finding of predominant diffuse muscle necrosis with evidence of regeneration and scant inflammatory cells consisting chiefly of macrophages. The treatment requires high-dose glucocorticoids combined with one or more immunosuppressants (methotrexate, intravenous immunoglobulins, rituximab) in 87% of cases. Despite immunosuppressant therapy, the prognosis is reserved, with only 44% of patients recovering normal muscle strength and 55% having persistent CK elevation >500 IU/L after 2 years of follow-up (34). When glucocorticoid therapy is contraindicated, intravenous immunoglobulins alone may be effective (35). A few cases of spontaneous recovery after statin discontinuation have been reported (26). Whether older age and statin exposure are associated with a better prognosis remains debated (34,36).

4. Management of patients who develop muscular symptoms during statin therapy

Routine CK monitoring in patients without risk factors or SAMSs is not recommended. The role for statin therapy in patients older than 75 years is controversial due to the absence of randomized controlled trials demonstrating efficacy for primary prevention in this age group, which is at high risk for adverse effects potentiated by polypharmacy and comorbidities (37). Two ongoing randomized controlled trials are evaluating whether statin therapy decreases overall mortality in patients older than 70 and 75 years, respectively.

When muscle symptoms develop during statin therapy (Figure 2), other causes should be sought, such as thyroid dysfunction, polymyalgia rheumatica, lumbar spinal stenosis, myopathy, strenuous exercise, exposure to other myotoxic agents, and drug-drug interactions. Persistent CK elevation to more than 4 times the upper limit of normal after statin discontinuation should lead to investigations for an underlying neuromuscular disease or for
NAM, including electromyography and a muscle biopsy (38). NAM should be considered in patients with severe muscle weakness and major CK elevation. An anti-HMGR antibody assay and a muscle biopsy provide the diagnosis.

The indication and risk/benefit ratio of statin therapy should be reevaluated routinely. In asymptomatic patients with moderate CK elevation (to less than 4 times the upper limit of normal), monitoring the CK levels may be sufficient. In other situations, if the cardiovascular risk is high and the need for statin therapy confirmed, discontinuation of the drug for 4-8 weeks followed by a return to the same drug at a lower dosage or the initiation of a different statin is a reasonable strategy. If it fails, switching to another class of lipid-lowering agents should be considered, with a preference for ezetimibe initially, followed by bile acid chelators, and fenofibrate. The monoclonal antibody evolocumab (PCSK9) is used in only a few cases, for instance in patients with familial hypercholesterolemia. Finally, vitamin D supplementation or the administration of ubiquinone (mitochondrial coenzyme CoQ10) may limit the side effects of statins.

5. Conclusion

SAMSs vary widely in frequency and severity, lack specificity, develop within the first month after treatment initiation or dosage intensification, and are expected to resolve within a few weeks after stopping the drug. The mechanisms of statin muscle toxicity, which govern the risk factors, include accumulation within the muscle to a degree that varies across statins and dosages, disorders in statin transport and hepatic metabolism, drug-drug interactions, genetic susceptibility factors, and underlying muscle fragility. Statins are valuable for the treatment of chronic diseases and comorbidities, notably chronic inflammatory rheumatic diseases, which are associated with an elevated cardiovascular risk. Statin therapy is
indispensable in patients at high or very high cardiovascular risk, in whom the benefits far outweigh the risks. In other situations, when statin therapy is discontinued due to toxicity, the indication and risk/benefit ratio should be reevaluated before returning to the same statin in a lower dosage or starting a different statin. When this strategy fails, other classes of lipid-lowering drugs should be considered. In patients with severe muscle symptoms, although rare, NAM should be sought by an anti-HMGCR antibody assay and a muscle biopsy, and immunosuppressant therapy should be provided if the diagnosis is confirmed.

**Disclosure of interest**

The author has no conflicts of interest to declare.
References


Table 1. Optimal LDL-cholesterol targets and interventions to be considered depending on the level of cardiovascular risk (HAS 2017 https://www.has-sante.fr).

<table>
<thead>
<tr>
<th>Level of cardiovascular risk</th>
<th>LDL-Ch target</th>
<th>First-line intervention</th>
<th>Second-line intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>SCORE &lt;1%</td>
<td>&lt;1.9 g/L (4.9 mmol/L)</td>
<td>Lifestyle changes</td>
</tr>
<tr>
<td></td>
<td>1%≤SCORE &lt;5%</td>
<td>&lt;1.3 g/L (3.4 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Type 1 or 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;40 years, no CVRFs, no target organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Type 1 or 2 diabetes</td>
<td>&lt;1.0 g/L (2.6 mmol/L)</td>
<td>Lifestyle changes + lipid-lowering medication</td>
</tr>
<tr>
<td></td>
<td>&lt;40 years and ≥1 CVRF or target organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40 years, no CVRF, no target organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BP ≥180/110 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>SCORE ≥10%</td>
<td>&lt;0.70 g/L (1.8 mmol/L)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type 1 or 2 diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥40 years and ≥1 CVRF or target organ involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe chronic kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Documented cardiovascular disease (secondary prevention)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LDL-Ch, LDL-cholesterol; CVRF, cardiovascular risk factor; BP, blood pressure
Table 2. Statin-related myotoxicity (SMR) phenotype classification developed in 2014 by an international panel of experts (17)

<table>
<thead>
<tr>
<th>SMR Class</th>
<th>Phenotype</th>
<th>Definition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CPK&lt;4·ULN</td>
<td>No muscle symptoms</td>
<td>1.5-26%</td>
</tr>
<tr>
<td>1</td>
<td>Myalgia, tolerable</td>
<td>Muscle symptoms without CK elevation</td>
<td>0.3-33%</td>
</tr>
<tr>
<td>2</td>
<td>Myalgia, intolerable</td>
<td>Muscle symptoms CPK&lt;4·ULN Complete resolution on dechallenge</td>
<td>0.2-2/1000</td>
</tr>
<tr>
<td>3</td>
<td>Myopathy</td>
<td>4·ULN&lt;CK&lt;10·ULN ± Muscle symptoms Complete resolution on dechallenge</td>
<td>5/100 000 patients-years</td>
</tr>
<tr>
<td>4</td>
<td>Severe myopathy</td>
<td>10·ULN&lt;CK&lt;50·ULN ± Muscle symptoms Complete resolution on dechallenge</td>
<td>0.11%</td>
</tr>
<tr>
<td>5</td>
<td>Rhabdomyolysis</td>
<td>CK&gt;10·ULN, renal impairment + muscle symptoms or CK&gt;50·ULN</td>
<td>0.1-8.4/100 000 patient-years</td>
</tr>
<tr>
<td>6</td>
<td>Necrotizing autoimmune myopathy</td>
<td>HMGCR antibodies, HMGCR expression in muscle biopsy, incomplete resolution on dechallenge</td>
<td>2/10⁶ per year</td>
</tr>
</tbody>
</table>

SMR, statin-related myotoxicity; ULN, upper limit of normal; CK, creatine kinase; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase
### Table 3. Risk factors for statin-related muscle toxicity

**Risk factors**

*Related to the patient*

- Age
- Female sex
- Low body mass index
- Alcohol abuse, other substance abuse, excessive intake of grapefruit juice or cranberry juice

*History of muscle abnormalities*

- CK elevation
- Unexplained myalgia
- Myopathy in the patient or family
- Statin-related myotoxicity

*Comorbidities*

- Acute infections
- Hypothyroidism
- Renal or hepatic dysfunction
- Diabetes
- Vitamin D deficiency
- Major surgery

*Treatments*

- High statin dosage
- CYP3A4 inhibitors: calcium-channel inhibitors (diltiazem, verapamil), macrolides, fusidic acid, cyclosporine, antifungal agents, protease inhibitors, amiodarone
- CYP2C9 inhibitors: omeprazole, fluconazole
- OATP1B1 inhibitors: fibrates, gemfibrozil, colchicine
Figure 1. Mechanisms of the therapeutic effects and myotoxicity of statins

Figure 2. Management of patients with creatine kinase elevation during statin therapy