RHEUMATOLOGY

Rheumatology 2020;0:1–5
doi:10.1093/rheumatology/keaa180

Concise report

Statin use and myopathy. Not always guilty

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Abstract

Objectives. Statins are the cornerstone of the treatment and prevention of cardiovascular disease but have been associated with muscular side effects, among others. If patients are not properly evaluated, statin discontinuation may take place, leaving patients' symptoms unresolved and precluding an effective cardiovascular treatment. The present study aims to describe the clinical characteristics, the diagnostic process and the final diagnosis of selected patients with suspected statin-induced myopathy, with quite different alternative diagnoses.

Methods. Among the 86 patients referred to our unit for evaluation since 2012, 6 patients with suspected statin-induced myopathy that was finally ruled out were selected as examples because of their illustrative value. All patients were evaluated in a Muscular Diseases Unit by myology experts, and additional testing was performed according to clinical suspicion.

Results. Of the six selected patients with suspected statin-induced myopathy, three had a neurogenic aetiology, two had vacuolar myopathies and one had severe hypothyroidism. Statins were permanently discontinued in two cases, with the treatment of one of the latter patients being continued with a protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

Conclusion. Not all patients taking statins who develop muscle complaints have statin-related myopathy. A thorough clinical evaluation and appropriate testing is warranted to avoid an unnecessary increase in cardiovascular risk.

Key words: statin, myopathy, muscle biopsy, necrotizing myopathy, anti-HMGCR

Rheumatology key messages

- Patients on statins presenting with any kind of muscle complaint should receive careful evaluation.
- Statin discontinuation should not be decided lightly, as it may have relevant cardiovascular consequences.

Introduction

Despite the fact that in randomized controlled trials statin therapy has adverse events rates similar to those of placebo groups, statin-related muscular symptoms are well described both in patient registries and in clinical practice. Statin-related adverse events affect around 7–29% of treated patients, often precluding the use of this treatment which is the cornerstone of the prevention and treatment of cardiovascular disease [1]. Several clinico-pathological phenotypes have been described. Myalgia, with or without elevated creatine-kinase (CK), may be the sole manifestation, with patients often complaining of heaviness, stiffness or cramps. Pain often involves lower limbs, and some patients may report tendonitis-associated pain [2]. Rhabdomyolysis, a severe form of acute muscle disease associated with statins, presents with a variable degree of weakness and high CK concentrations as well as with myoglobinuria and possible renal impairment. Self-limited toxic myopathy has variable severity, with many patients presenting with proximal weakness and high CK levels, and usually improves after statin discontinuation. Contrarily, immune-mediated necrotizing myopathy, a true autoimmune myopathy, presents with progressive proximal muscle weakness and CK values over 10–100 times the upper limit, often with positive 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) antibodies. It

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Submitted 5 November 2019; accepted 19 March 2020

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does not improve with statin withdrawal and requires immunosuppressive treatment [3].

Some predisposing factors, such as the existence of a previously diagnosed neuromuscular disease, hypothyroidism or family history of myopathy, have been proposed [4], but they are not supported by strong quality evidence and fail to identify many patients that will develop statin-related muscle complaints. Lack of adequate patient information about statin safety and effectiveness may influence patient expectations about treatment and act as a confounding factor through the nocebo effect [5]. Furthermore, not every patient taking statins that develops muscle symptoms will necessarily present statin-related muscle disease. All these reasons may lead the clinician, too often, to wrongly attribute patients' symptoms to these drugs.

In the past 7 years, a total of 86 patients with suspected statin-related myopathy have been referred to our unit for evaluation. A systematic approach including medical history, thorough physical examination, CK levels, EMG and HMGCR antibodies was performed. Whole-body MRI as well as muscle biopsy were performed only in selected cases. Of these patients, eight received the final diagnosis of immune-mediated necrotizing myopathy, all of them exhibiting high titres of anti-HMGCR antibodies. Most patients in this series presented with mild complaints such as myalgia or minimally raised CK levels that resolved after changing the statin or modifying its dosage. The six patients presented here were selected among the 86 cases as examples because of their illustrative clinical value, thus demonstrating that the statin is not always guilty.

Case description

Case 1

In 2012, a 72-year-old man with a history of long-term diabetes mellitus, hypertension and ischaemic cardiopathy, treated with 40 mg of atorvastatin since 2010, developed myalgia in his lower extremities and elevated CK reaching a maximum of 613 IU/l. Statin muscle toxicity was suspected, and atorvastatin was withdrawn without improvement of the pain or CK normalization. In this context, the patient was referred to our muscle unit, where mild atrophy of the bilateral quadriceps with preserved strength was noted. Neurological examination was normal, with osteotendinous reflexes (OTR) present and negative Lasègue and Bragard signs. EMG only showed signs of bilateral L5 radiculopathy, without a myopathic pattern, and a quadriceps biopsy was performed, showing denervation and reinnervation. HMGCR antibodies were negative. A lumbar MRI showed L2–L5 disc protrusion causing vertebral canal stenosis and bilateral radicular compression. Statin therapy was reintroduced, and the patient was referred to traumatology and managed with analgesia, physical therapy and occasional CS epidural injections, with pain improvement and progressive CK normalization after a few months.

Case 2

A 69-year-old man with poorly controlled diabetes mellitus and hypertension who had presented an ischaemic stroke in the territory of the left medial cerebral artery in 2002 and another left thalamic stroke in 2006, both without sequelae, had been taking 80 mg atorvastatin since 2010. In 2014, he presented with lower extremity myalgia and proximal weakness of 1 month in duration, with a peak CK of 1290 IU/l, for which he was referred to our unit. On physical examination OTR were absent in the lower extremities, and EMG was compatible with right-side L5 radiculopathy. A quadriceps muscle biopsy showed scarce necrosis and prominent reinnervation, HMGCR antibodies were negative and a lumbar MRI showed degenerative changes affecting L2–L3, L3–L4 and L4–L5, with posterior L5–S1 protrusion and right sided L5 root compression, as well as mild lumbar canal stenosis. Statin therapy was restarted, and the patient analgesia was adjusted. Although CK level improved until eventual normalization, the patient's pain did not improve initially, and he was started on physical therapy with some degree of improvement.

Case 3

A 60-year-old man who had been treated with 20 mg simvastatin for 12 months because of high blood cholesterol presented with a 10-month complaint of myalgia in the upper and lower limbs as well as intolerance to exercise, with a peak CK of 2147 IU/l. Statin treatment was withdrawn without improvement of the symptoms, and the patient was referred for evaluation to our unit for evaluation in 2015. His physical examination was unremarkable, with normal strength and OTR. A deltoid muscle biopsy did not present any pathological changes. On blood analysis, the thyroid-stimulating hormone was 78.9 mIU/l, with low free T4 and negative HMGCR antibodies. Hypothyroidism was diagnosed and the patient was started with substitutive therapy, presenting complete symptom remission and CK normalization. Statin therapy was restarted with good tolerance.

Case 4

A 67-year-old woman with previously diagnosed severe dyslipidaemia treated with 10 mg simvastatin presented with a 10-month history of weakness and intolerance to exercise in 2015. The symptoms did not improve after statin withdrawal shortly after symptom onset. The physical examination was unremarkable, but the patient had high a CK value of 662 IU/l with negative HMGCR antibodies. A quadriceps muscle biopsy presented only signs of reinnervation, and therefore, statin-related muscle injury was ruled out. The patient was referred to a traumatology specialist to continue study while statin therapy was reintroduced. CK levels had descended to normal levels in the next follow-up blood analysis after 2 weeks. The only study performed by the traumatologist shortly afterwards was a lumbar X-ray where L2 height loss and diminished intervertebral disc spaces affecting

all the lumbar vertebrae were observed. Analgesia was started with pain improvement, and treatment for osteoporosis was introduced.

Case 5

A 70-year-old man with a history of diabetes, dyslipidaemia and chronic kidney disease had been treated with 20 mg simvastatin for 4 years prior to evaluation in 2015. He complained of myalgia, distal weakness and intolerance to exercise, as well as worsening dysphagia, with persistently elevated CK over the past year, reaching a maximum of 690 IU/l. On physical examination he had proximal and distal weakness. EMG showed both signs of axonal polyneuropathy and a myopathic pattern and MRI showed distal posterior compartment oedema in both legs. A deltoid biopsy was performed in which cytoplasmatic vacuoles were present, some of which were rimmed, with negative periodic acid–Schiff and positive desmine immunohistochemistry (Fig. 1A and B). HMGCR antibodies were negative. The patient was diagnosed with desminopathy, and statin therapy was discontinued.

Case 6

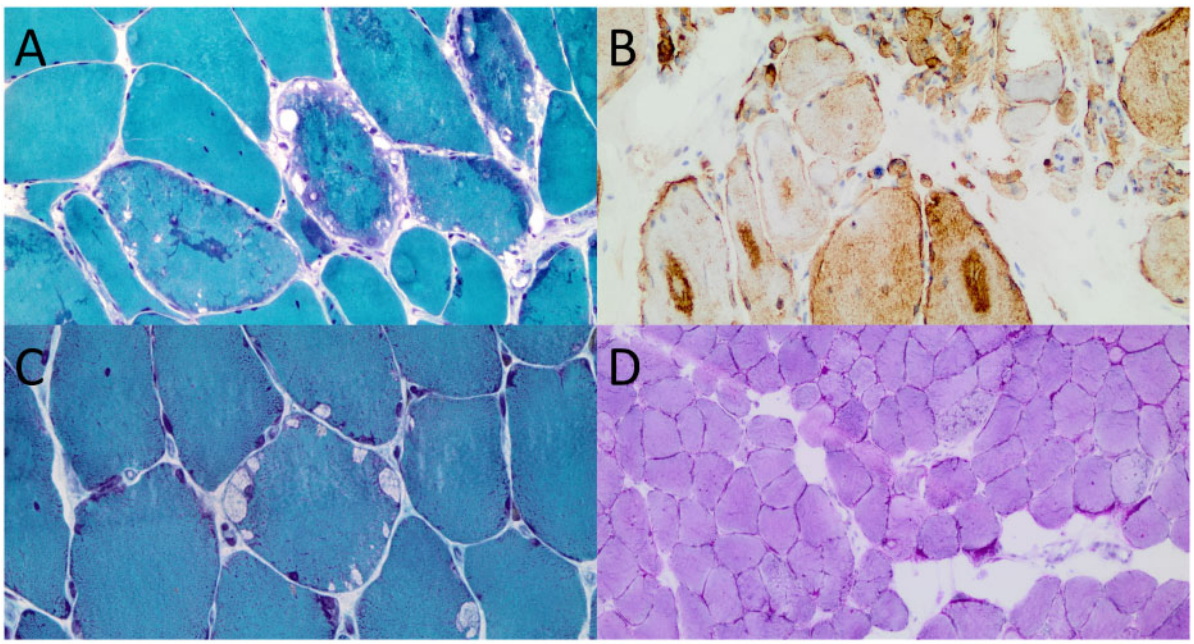
A 65-year-old man with well controlled hypertension and prior ischaemic cardiopathy treated with 20 mg simvastatin since 2000 was evaluated in 2015 because of intolerance to exercise that had developed in the last 3 years. He did not explain symptoms suggestive of second wind phenomenon [6] and the maximum CK value was 838 IU/l. Evaluation at our unit showed proximal weakness in both the upper and lower limbs. A deltoid biopsy revealed subsarcolemmal vacuoles that were periodic acid–Schiff positive (Fig. 1C and D). The myophosphorylase histochemical reaction was normal. HMGCR antibodies were negative and alpha-1,4-glucosidase activity was normal in the dry blood test, but phosphofructokinase activity was low on two separate occasions, and Tarui disease was diagnosed. Statin therapy was not reintroduced, and the patient received protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor treatment.

Discussion

In this report, we describe six patients with suspected statin-induced muscle injury who were referred to our unit for evaluation. After careful clinical evaluation and proper diagnostic testing by experts in myology, these patients were diagnosed with non-statin-related diseases. This is in contrast to the decisions of the treating physicians who had discontinued the drug in all of the patients, despite most having cardiovascular risk factors other than dyslipidaemia, and three had already had previous cardiovascular events.

The introduction of statin therapy has notably reduced both cardiovascular morbidity and mortality in the general population at risk, and there is strong evidence supporting its use in selected patients [7]. The previously mentioned discordance among randomized

Fig. 1 Picture of relevant biopsy histology



Cell size variability and cytoplasmatic inclusions are observed (**A**). These inclusions are desmine-positive on immunohistochemistry (**B**). Subsarcolemmal vacuoles are shown (**C**), corresponding to PAS-positive deposits (**D**). PAS: periodic acid–Schiff.

controlled trials and registries and clinical practice may be due to different reasons. After thoroughly examining previously published randomized controlled trials, Ganga *et al.* [8] found that most of these trials did not actively evaluate muscle problems, and even when they were registered, they were not properly described. Nevertheless, muscle problems were described in about 12% of patients both in the treated and the placebo group. On the other hand, in their meta-analysis, Yebyo *et al.* [9] found that statins as a class showed a statistically significant risk of increase of myopathy (relative risk 1.08, 95% CI 1.01–1.15), even though they did not describe its nature and nor did they find an association with specific statins. Finally, according to the European Atherosclerosis Society Consensus Panel, patient registries and clinical experience indicate that around 7–29% of patients complain of statin-associated muscle symptoms, greatly contributing to the abandonment of treatment and worsening of cardiovascular outcomes [1].

These discordant findings may be partially explained by the different phenotypes attributed to statin-related myopathy [3]. These phenotypes include any degree of benign myalgia, asymptomatic or paucisymptomatic CK elevation or self-limited toxic myopathy that improves with drug withdrawal, up to the more severe and even life-threatening forms such as rhabdomyolysis, an acute massive muscle necrosis that may lead to acute kidney injury [10], or immune-mediated necrotizing myopathy, with continuing myofiber necrosis despite statin cessation, requiring aggressive and prolonged immunosuppressor treatment [11].

Thus, taking into account its clinical heterogeneity and potential severity of statin-related myopathy, its real incidence might be somewhere in-between what has previously been reported. It is important to correctly identify patients with statin-related muscular problems, as both statin continuation or cessation, when done lightly and without enough evidence, may have deleterious consequences, either by worsening a potentially life-threatening myopathy or by increasing cardiovascular risk, respectively. Before starting statin treatment, a proper cardiovascular risk assessment should take place in order to ensure that the drug is indicated. Lifestyle changes should be encouraged, and potential side effects and their frequency should be explained to the patient in order to adjust patient expectations and avoid the nocebo effect. A comprehensive revision of the patient current medication should be performed to rule out potential drug interactions, considering alternatives to statin treatment such as ezetimibe or a PCSK9 [12]. Thyroid function, as well as renal function should be investigated, and an adequate statin dose should be started, as previous evidence suggests that high doses are associated with higher myopathy rates [13]. Increased caution should be adopted with older patients, particularly in those with low BMI, although treatment should be started if it is indicated, as well as with users of cocaine or alcohol or affected or with hepatic or renal insufficiency [4, 14, 15].

Whenever a patient taking statins reports muscle complaints, clinicians should perform a meticulous clinical examination including muscle strength and OTR, and exclude secondary causes such as exercise or trauma, hypothyroidism, drug abuse, pharmacological interactions, neurogenic conditions or the presence of a well-defined myopathy [3, 14].

Contrarily to CK or aldolase elevation, which are unspecific and may rise in a variety of neurogenic conditions, determination of anti-HMGCR antibodies, which are positive in 75% of patients with immune-mediated necrotizing myopathy [16], may prove helpful when determining whether or not statins may be the trigger of a patient's clinical picture. While isolated myalgia may not warrant statin discontinuation, more serious symptoms should prompt statin withdrawal and strength and CK monitoring. If symptoms improve, either repeated challenge with statins may be attempted in order to assess the causality of muscle pain [17] or an alternative lipid-lowering agent may be introduced. Otherwise, the patient should be referred to a myology expert for evaluation.

An EMG study, when performed by an expert, represents another important element in this setting, and can lead to the suspicion and diagnosis of radiculopathy, polyneuropathy or lumbar canal stenosis. Likewise, MRI may be highly useful, not only in the evaluation of a suspected radiculopathy or lumbar canal stenosis, but also in detecting muscular oedema or atrophy, further supporting a myopathic aetiology of the symptoms. Finally, muscle biopsy can be of great interest in the study of the statin-associated muscle disorders, showing either the characteristic immune-mediated necrotizing myopathy pattern or other myopathic changes or alterations pointing to other aetiologies, as was the case with the patients in our series.

Our six patients were from a cohort of 86 of patients referred since 2012 with the suspicion of statin-related myopathy. No specific criteria were used to select these patients other than their use as examples because of their illustrative value. All the patients were thoroughly evaluated, with a meticulous clinical history and examination, a basic blood analysis including thyroid function, an immune panel including anti-HMGCR antibodies and, finally, a muscle biopsy in order to confirm or rule out the suspected condition. In three patients, muscle biopsy showed evidence of changes suggestive of denervation, reinnervation or both, pointing to a neurogenic aetiology. In two other patients, an unsuspected vacuolar myopathy was observed, one corresponding to a type VII glycogenosis or Tarui disease and the other to a myofibrillar myopathy, a desminopathy. The last patient in our series presented a normal muscle biopsy, but was diagnosed, after routine work-up, with hypothyroidism and treated accordingly.

Even after statin-related muscle injury had been reasonably ruled out, two of the patients that had been diagnosed with primary muscle disease did not restart statins, probably owing to the existing fear that these drugs may not be safe in patients with myopathy, despite the fact that some evidence exists to the contrary [18]. One of the patients was started on a PCSK9 inhibitor, an effective and well-tolerated alternative to statins in this group of patients [4].

Conclusion

This case series reinforces the need for patients receiving statins complaining of any kind of suspected muscle disturbance to always be properly assessed and carefully evaluated before blaming the drug as the causal agent, in order to avoid both unjustified withdrawal of an important treatment and to prevent other causes of the symptoms remaining unnoticed.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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