

Statin-related myopathies

David Hilton-Jones

Correspondence to

Dr David Hilton-Jones, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, OX3 9DU, UK; david.hilton-jones@ndcn.ox.ac.uk

Accepted 8 February 2018

ABSTRACT

Statins are the Marmite ('You either love it or hate it!') of the drug world, both in terms of therapeutic benefit and risk of side effects. Proponents think that they are potential life-savers, opponents that their main benefit is lining the pockets of pharma. Some consider side effects to be a major issue, outweighing any therapeutic benefit, others that they are rare and essentially innocuous. Statin-induced myalgia is relatively common but often mild and for most people does not limit treatment. In others, reducing the dose or changing the preparation may help. In all, withdrawal of the statin leads to resolution. Statin-induced rhabdomyolysis, most often precipitated by drug–drug interaction, affects only a tiny proportion of statin users, but because of the widespread prescribing of statins is an important clinical problem. Statin-induced immune-mediated necrotising myopathy represents a novel disease mechanism and clinically mimics forms of myositis. Resolution often requires immunosuppressant drug treatment, as well as statin withdrawal.

INTRODUCTION

Statins are the most widely prescribed drugs in the western world. In the UK alone (population 65 million), over 6 million people take them, and if recent therapeutic advisory guidelines are followed that number could exceed 12 million—most of whom are middle-aged or elderly and often on polypharmacy. Thus, even a rare side effect may occur relatively commonly, and my own experience is that statins are now the most common reason for acute hospital admission with rhabdomyolysis.

This is not a systematic Cochrane-style review of the literature relating to statins and myopathy. Such a task would be daunting: a simple literature search combining the terms *statins* and *myopathy* for the last decade alone produces over 12 000 papers, equating to approximately one new paper every 3 days. As noted below, much such data are uninterpretable. This review also does not cover the sometimes controversial indications

for statin therapy or give any detail about the molecular or immunological mechanisms underlying some forms of statin-induced myopathy. Rather, it is intended to give a pragmatic guide to jobbing neurologists about the myopathic complications of statins that they may well come across in everyday practice and guidance for the use of statins in patients who already have a myopathic disorder.

DODGY DOSSIERS

Many neurologists are used to dealing with diseases so uncommon that the number of authors of a paper exceeds the number of patients worldwide known to have the condition. It may therefore seem a luxury to be dealing with an issue—the side effects of statins—that can be studied in meta-analysis of individual trials with tens of thousands of patients, with combined numbers in the millions. Surely such data give unequivocal answers? But sadly no, as the continuing war between the pro-tatin and antistatin lobbyists demonstrates (<http://www.cardiobrief.org/2016/09/15/the-lancet-versus-bmj-dispatch-from-the-statin-wars/>). Meta-analysis data suggest that there is no significant difference in the prevalence of muscle symptoms between statin-treated and placebo groups. For example, in a meta-analysis of trials involving over 100 000 individuals, the incidence of muscle symptoms was 12.7% in the statin-treated group and 12.4% in the placebo group, an insignificant difference.¹ However, the problem is that in most of the studies, the quality of data collection and interpretation was so poor that conclusions become meaningless.^{1 2} Errors include reliance on ill-defined self-reported symptoms, no clinical assessments of muscle symptoms and function and meaningless definitions based on serum creatine kinase (CK) results (eg, defining myositis on the basis of CK level and not pathology). A notable exception was the STOMP (effect of statins on skeletal muscle function and performance) study, a double-blind trial with detailed pretrial definitions of



► <http://dx.doi.org/10.1136/practneurol-2017-001848>



To cite: Hilton-Jones D. *Pract Neurol* 2018;**18**:97–105.

symptoms and expert clinical assessment of muscle function. The conclusions were that atorvastatin was associated with a significantly increased frequency of myalgia and an increased average serum CK concentration, but no effect on strength or exercise performance.³ A recent major review of the literature concluded, 'Typically, treatment of 10 000 patients for 5 years with a standard statin regimen (such as atorvastatin 40 mg per day) would be expected to cause about five cases of myopathy', implying a very low incidence of muscle problems.⁴ The authors were challenged that they were implying that 'statin myalgia does not exist',⁵ to which they responded 'that the *annual excess* (my italics) of muscle-related problems actually caused by (rather than being attributed to) statin therapy is no more than about 10–20 cases per 10 000 treated individuals, with only about one of those cases associated with substantial elevations in CK concentrations (ie, myopathy) and requiring statin therapy to be stopped'.⁶ Meta-analysis is fine in concept but may fail when the input data are unreliable.

Muscle symptoms are perhaps much more common in everyday clinical practice than reported in trials. One suggestion is that trials include highly selected patients, at overall lower risk of developing complications. Another is that adverse publicity available to the general public, in the lay press and electronic media, concerning potential side effects may induce a nocebo effect—psychologically mediated rather than pharmacologically mediated symptoms.⁷

In brief conclusion, an apparently vast amount of data, because of flawed collection and conception, offers little insight into the nature and frequency of possible statin-induced muscle problems. Overall, there is good evidence that statins may cause muscle pain (myalgia) that this may or may not be associated with an increase in serum CK, but is rarely associated with impaired muscle function. Almost invariably, it responds to statin withdrawal and has no long-term adverse consequences. However, there is unequivocal evidence from individual reports that statins may induce rhabdomyolysis, but it is a relatively rare and so meta-analysis studies typically fail to confirm the association. For the same reason—its rarity—none of the past meta-analysis studies could show the now well-recognised statin-induced immune-mediated necrotising myopathy (discussed later). And yet, because of the vast numbers of people receiving statins, these problems are of great clinical importance.

ARE THE STATINS NECESSARY?

As discussed below, most statin-related myopathies are self-limiting and resolve on stopping the statin. Furthermore, most patients with a pre-existing myopathy can safely take statins. The question that obviously must be asked, when considering whether to reintroduce a statin after a myopathic problem or starting them for the first time in somebody with a

Box 1 Statin-related myopathies

- ▶ Myalgia+/-raised serum creatine kinase
- ▶ Rhabdomyolysis
- ▶ Immune-mediated necrotising myopathy

myopathy, is, 'Does this person really need to take a statin?' That is usually not a question for the neurologist, who will defer to the expertise of others. The ongoing controversies concerning statin use have been noted above. Consideration should be given to alternative management, including diet and non-statin drugs such as fibrates. Novel, but currently very expensive, approaches to lowering serum cholesterol include PCSK9 inhibition.⁸ But there remains a significant number of vascular high-risk patients for whom the potential risks from restarting statins may be justified.

STATIN-RELATED MYOPATHIES

There are three currently recognised forms of statin-induced muscle dysfunction (box 1): myalgia, rhabdomyolysis and immune-mediated necrotising myopathy.

Myalgia

Myalgia is by far the most common symptom associated with statins. It is the symptom that has probably generated the most lay interest and is often cited as a major contraindication, or at least concern, to the use of statins. Yet its frequency is the issue that the existing literature has failed to satisfactorily answer; a voluminous literature has by and large concluded that the prevalence of myalgia is much the same in statin and placebo treated groups. However, with the exception of the STOMP trial, the literature has to be largely dismissed because of inadequate approaches to data collection.³ Myalgia is an extremely common complaint in general practice, and the nocebo effect in statin users may be relatively common.⁷ The STOMP study used stricter definitions than preceding studies, including the obvious temporal relationship between starting a statin (atorvastatin in this study) and the onset of myalgia, resolution on stopping the statin and recurrence of the same symptoms on rechallenge. Furthermore, those taking statins had a consistent pattern of myalgia, mainly involving the proximal lower limb muscles, whereas muscle symptoms in the placebo group, including myalgia, were more diverse. In STOMP, 19/203 (9%) of people treated with atorvastatin had myalgia. None of them had evidence of impaired strength or exercise function. The serum CK was modestly elevated in 40/203 patients on atorvastatin but it was not stated how many of the 19 patients with myalgia had a raised CK. No patient had a marked (>10 times upper limit of normal) increase in CK. Numerous other studies have shown that statins may increase CK, but it is difficult to interpret these data because of very poorly defined study methods. It

Box 2 Managing statin-induced myalgia

- ▶ Consider vitamin D supplementation
- ▶ Withdraw statin
- ▶ Lower the dose
- ▶ Try an alternative statin

is clear that not all patients with myalgia have a raised CK and that not all those with a raised CK have any muscular complaints.

Myalgia on physical exercise may be more prominent in those on statins, without certain evidence of impaired muscle function,⁹ but statins in professional athletes may limit performance.¹⁰

There has been much debate as to whether low concentrations of coenzyme Q (CoQ) or vitamin D increase the risk of myalgia and if their supplementation improves it. Statins inhibit the metabolic pathway for which CoQ is a distal component and statins lower tissue CoQ concentrations. However, the evidence to date provides little evidence of a significant association with muscle symptoms and does not support using CoQ supplements.¹¹

Several studies have reported an association between myalgia and low serum vitamin D concentrations, with symptom improvement with supplementation to restore normal levels,^{12–15} whereas others found no association.^{16–17} We clearly need further studies but in the meantime it is appropriate to check serum vitamin D concentrations in people with myalgia and to give replacement therapy as required (box 2).

An occasional issue is the patient with a 'very high' serum CK, either with or without muscle symptoms, and the concern as to whether persistence may eventually lead to permanent muscle damage. There is little evidence to suggest that any such damage ensues but many physicians feel uncomfortable with a serum concentration above, say, 1000 iu/L (depending on definitions/age/sex/race, this may be 2–5 times the quoted upper limit of normal). The possibility of a statin-induced immune-mediated necrotising myopathy is discussed below. In practice, in such patients with marked CK elevation, it is probably reasonable to follow the same path as with a patient with troublesome myalgia—with or without a raised CK—discussed below.

Patients often tolerate mild myalgia and non-specific aches and pains. If not, the options include a trial of vitamin D supplementation if serum concentrations are low, withdrawal of the statin, dose reduction or trial of a different statin (box 2). If there is uncertainty as to whether it is a statin-induced problem, or the serum CK is very high, then I suggest stopping the statin and observing the response. For milder symptoms, one might in the first instance just try reducing the dose. If the myalgia or high CK persists, then alternative

explanations need to be sought. A frequent practical problem is that serum CK is rarely measured before starting a statin. The elevated CK may therefore have preceded the introduction of the statin and reflect a pre-existing myopathy that may have been asymptomatic, or have been oligosymptomatic, and the significance of symptoms unrecognised. There are cases in the literature, and in my own practice, of McArdle's disease and other genetic myopathies that have been identified only when patients reported muscle problems after starting a statin, but subsequent assessment revealed that they had in fact had longstanding but unrecognised classical symptoms.

If myalgia resolves on statin withdrawal, and assuming that the patient needs to be on a statin, then the options include either reintroducing the same statin at a lower dose, with monitoring of clinical response, serum CK and adequate reduction in cholesterol or trying an alternative statin. Despite some reports that a particular statin appears to cause fewer problems than others or theoretical arguments about differing lipid solubility between different statins, there is little evidence to favour any one agent, and the choice can be made on personal experience and, increasingly, availability of specific drugs from local formularies, determined in part by cost. If need be, several different drugs can be tried.

Polymorphisms in genes coding for transporter proteins have been associated with an increased risk of statin-induced myalgia and rhabdomyolysis. An *SLCO1B1* gene polymorphism (S21T>C) particularly associates with simvastatin-induced problems.¹⁸ However, the situation is more complex than that and sex and ethnicity are also relevant. Thus, the same *SLCO1B1* polymorphism has recently been shown to be associated with increased myotoxicity in Chinese people receiving rosuvastatin.¹⁹ There is as yet no evidence to support the cost effectiveness of screening for this polymorphism or for those in other genes, before starting statins.

In contrast to statin-induced immune-mediated necrotising myopathy, discussed below, the presence of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibodies is not associated with myalgia.²⁰

Rhabdomyolysis

While there is no universally accepted definition, rhabdomyolysis describes the widespread breakdown of muscle fibres, which releases CK and myoglobin into the circulation. The kidneys excrete myoglobin and this may discolour the urine dark brown/red—frequently referred to as cola-coloured or tea-coloured urine—and often misdiagnosed by visual inspection and dipstick testing as haemoglobinuria. Involvement may be restricted to one muscle or group, but is usually more widespread. The typical clinical presentation is with pain, weakness and sometimes muscle swelling evolving subacutely over hours to a few days

Box 3 Case history—rhabdomyolysis

- ▶ 78-year-old man
- ▶ Had a history of chronic obstructive pulmonary disease and dilated cardiomyopathy
- ▶ Taking furosemide, alendronate and simvastatin 40 mg per day (for 2 years)
- ▶ Chest infection treated with erythromycin
- ▶ Within 3 days developed proximal lower limb pain and weakness
- ▶ Unable to stand because of proximal weakness
- ▶ Serum creatine kinase (CK) on admission 15 175 iu/L (normal < 350)
- ▶ Simvastatin and erythromycin stopped
- ▶ Serum CK returned to normal after 2 weeks
- ▶ Strength recovered within 6 weeks

(see Case History). With a typical clinical picture and gross elevation of the serum CK, the diagnosis is usually straightforward. There is not always visible urine discolouration, and there is no great value in estimating urinary myoglobin. As with the literature on statins and myalgia, that referring to statin-induced rhabdomyolysis is also of poor quality, with definitions that would not be accepted by muscle specialists (eg, raised serum CK without muscle symptoms). Despite these reservations, there is no doubt that any statin at sufficiently high dose may precipitate rhabdomyolysis. Some may be more of a risk than others, and cerivastatin was withdrawn from the market after reports of a cluster of cases, including several deaths in a short period of time. The exact mechanism of statin-induced rhabdomyolysis is unknown but probably relates to a consequence of downstream effects from blockage of the metabolic pathway inhibited by statins at the HMGCR enzyme. The most important factors triggering rhabdomyolysis are high dose and iatrogenically induced high serum concentrations precipitated by drugs that inhibit statin breakdown (box 3). Additional risk factors, knowledge of which is not particularly helpful clinically, include older age, hypothyroidism, renal impairment, other comorbidities and polypharmacy.

Statins, with the exception of pravastatin, are metabolised by the cytochrome P-450 enzyme system, as are numerous other therapeutic drugs. There is a huge potential for drug-to-drug interactions; in the present context, this means that there are many commonly used drugs that inhibit statin metabolism and may therefore precipitate rhabdomyolysis. Clinically, the major problems relate to concurrent use of various cardiovascular drugs, fibrates (often coprescribed with statins in those with severe hypercholesterolaemia and other vascular risk factors) and antimicrobials; box 4 lists some of the more common culprits, but for excellent comprehensive summaries see Wiggins *et al* and Hylton *et al*.^{21 22} Cardiovascular drugs are of course

Box 4 Some commonly prescribed drugs that may precipitate rhabdomyolysis when coprescribed with statins (for comprehensive reviews, see Wiggins *et al* and Hylton *et al*.^{21 22})**Fibrates**

- ▶ Gemfibrozil

Cardiovascular drugs

- ▶ Amiodarone
- ▶ Amlodipine
- ▶ Diltiazem
- ▶ Verapamil

Antimicrobials

- ▶ Azole antifungal agents
- ▶ Macrolides (eg, erythromycin, clarithromycin)
- ▶ Ciprofloxacin

Others

- ▶ Ciclosporin

likely to be prescribed long term, whereas most antimicrobial agents are used only briefly; arguably in the latter situation, the statin could be temporarily withheld if there is no alternative antibiotic. Cardiovascular drugs such as amlodipine can be used safely if the dose of statin is restricted (eg, simvastatin restricted to maximum dose of 20 mg with amlodipine).²¹ Besides these two major drug groups, many other drugs may precipitate rhabdomyolysis through cytochrome p450 inhibition;²³ these include ciclosporin, which is fairly often used in association with statins (eg, for immune suppression following kidney transplantation in a diabetic).

The management of statin-induced rhabdomyolysis primarily involves statin withdrawal (box 5). Myoglobinuria carries the risk of acute tubular necrosis and renal failure. Although forced alkaline diuresis may seem appropriate in theory, there is little evidence to support it and I simply recommend relatively high fluid input, to induce diuresis, for several days. Patients may also need pain relief. Particularly in the elderly, it is important to have early physiotherapy input to reduce risk of contractures and to maintain range of movement when very weak and then to aid mobilisation at the earliest opportunity.

Box 5 Management of statin-induced rhabdomyolysis

- ▶ Withdraw statin
- ▶ Fluid-induced diuresis
- ▶ Monitor renal function and serum creatine kinase
- ▶ Pain relief
- ▶ Physiotherapy

Muscle biopsy is unnecessary if the clinical diagnosis is secure. Rarely, and arguably most often considered because of ignorance of the mechanism or failure to take a detailed drug history, muscle biopsy may help to exclude an inflammatory myopathy that would require use of corticosteroids. Dermatomyositis can have a similar subacute onset and could conceivably be confused with drug-induced rhabdomyolysis. Statin-induced immune-mediated necrotising myopathy would rarely present so acutely.

An episode of statin-induced rhabdomyolysis does not necessarily contraindicate the reintroduction of statins. If there is a recognised specific interaction (eg, simvastatin and erythromycin, see Case Report), then there is no reason to withhold the original statin. In other situations (eg, simvastatin and amlodipine), it may be appropriate to reduce the dose of amlodipine. Pravastatin, which is not cytochrome p450 metabolised, may be considered in combination with other drugs that are cytochrome p450 metabolised, but it is not free of drug-to-drug interactions and, for example, is contraindicated in combination with gemfibrozil, since both are metabolised via OAT P1.

Immune-mediated necrotising myopathy

Although the least common statin-related myopathy, this is of considerable clinical importance and research interest. Whereas the disorders discussed earlier resolve on statin withdrawal, this condition may progress and requires specific treatment (immunotherapy).

Most immune-mediated myopathies are characterised pathologically by major inflammatory infiltrates in muscle, designated myositis, including dermatomyositis, polymyositis and antisynthetase syndromes. Clinically, they are characterised by progressive proximal weakness, and many are associated with myositis-specific or myositis-associated antibodies in the serum. The immune-mediated necrotising myopathies are a recently delineated group of disorders with a similar clinical presentation to myositis (ie, progressive weakness) but muscle biopsy shows few or no inflammatory infiltrates despite frequent necrotic and regenerating muscle fibres (figure 1). Critically, like myositis, they respond to immunotherapies. There are three main forms of immune-mediated necrotising myopathies; those associate with anti-signal recognition particle antibodies, those with anti-HMGCR antibodies and seronegative cases.

The link between statin use and the development of progressive weakness, due to an immune-mediated necrotising myopathy associated with anti-HMGCR antibodies, was initially shown in 2010,²⁴ but there have since been numerous confirmatory reports.^{25–27} Such patients may have been taking statins for months or occasionally years. They then develop slowly progressive proximal, mainly lower limb, weakness with a very high serum CK (typically >5000 iu/L). Some have myalgia, but the process may be painless.

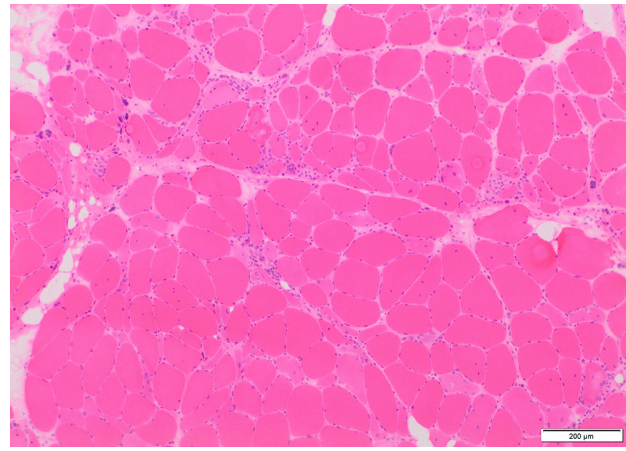


Figure 1 H&E section showing widespread necrotic and regenerating fibres, but no significant inflammatory infiltrates. Photograph courtesy of Dr Monika Hofer.

The symptoms usually progress despite stopping the statin. In two cases reported in this edition of *Practical Neurology*,²⁸ the myopathy resolved on statin withdrawal without additional treatment; however, in an interesting variation on the theme, the myopathy recurred in one patient when statins were introduced 4 years later did not resolve on statin withdrawal the second time and so required immunosuppressant treatment. The muscle biopsy shows features of an immune-mediated necrotising myopathy. Intensive treatment with corticosteroids, with or without second-line agents such as methotrexate, may be effective, but there is increasing evidence that many patients in addition require intravenous immunoglobulin to induce remission, and in some patients, this has been used as monotherapy.²⁹ There is also evidence that younger patients may have more severe disease and be more resistant to therapy than older patients, which may influence therapeutic approaches.³⁰

Anti-HMGCR associated immune-mediated necrotising myopathy is strongly associated with HLA DRB 1*11:01.³¹

There is no evidence that HMGCR antibodies are directly pathogenic. Increasingly, they have been found in association with immune-mediated necrotising myopathies in patients who have never been exposed to statins, including children. Furthermore, there is mounting evidence of an increased incidence of cancer in people with HMGCR related immune-mediated necrotising myopathy, with or without a history of statin exposure.³² This needs further study, but on current evidence, it seems reasonable practice to consider the possibility of underlying malignancy in adults presenting with immune-mediated necrotising myopathy with HMGCR antibodies, as one should do with patients presenting with dermatomyositis. Thus, patients need clinical assessment, imaging (CT scan of chest/abdomen/pelvis or positron-emission tomography scanning), mammography, serum tumour

Box 6 Statin-induced immune-mediated necrotising myopathy

- ▶ Onset: months to years after starting statins
- ▶ Progressive proximal (lower limb) weakness
- ▶ Very high serum creatine kinase (>5000 iu/L)
- ▶ Biopsy—necrotising myopathy with little or no inflammation
- ▶ Serum 3-hydroxy-3-methylglutaryl-CoA reductase antibodies
- ▶ Often a poor response to corticosteroids
- ▶ May respond to intravenous immunoglobulin

markers; clinicians should maintain suspicion for 1–2 years after first presentation. The risk is probably greater in older patients.

The diagnosis of anti-HMGCR immune-mediated necrotising myopathy may not be considered initially because of the lack of an immediate temporal relationship with the starting of statins. When it is, identifying the characteristic features (box 6) should lead to rapid diagnosis. The statin should be stopped. If the weakness is mild, it is appropriate to wait a few weeks to see if there is spontaneous improvement, although that is unlikely.

Persisting myalgia after statin withdrawal

A sometimes challenging problem is the patient who develops myalgia when put on statins and the symptoms persist despite drug withdrawal. At present, the only recognised pathological mechanism to explain a persisting myopathy after statin withdrawal is the syndrome of immune-mediated necrotising myopathy, described above. Those patients may or may not have myalgia, but invariably have progressive weakness, elevated (usually marked) serum CK and HMGCR antibodies. The more common problem is the patient with persisting myalgia without weakness. Box 7 shows an approach to their assessment.

It is of course important to clarify that the myalgia did indeed start after starting the statin; noting that statin-induced myalgia typically develops very shortly after starting the treatment or increasing the dose. Myalgia developing months or years after starting treatment is much less likely to be related. As noted above, myalgia due to a pre-existing but unrecognised disorder may apparently become symptomatic only

Box 7 Persisting myalgia after statin withdrawal**Consider:**

- ▶ Pattern of myalgia
- ▶ Serum vitamin D
- ▶ Serum creatine kinase
- ▶ Electromyography
- ▶ Biopsy

when the patient and doctor are looking out for statin-related problems.

The specific characteristics, and in particular the distribution of the myalgia, can be helpful. As noted in the STOMP study, statin-induced myalgia mainly affects the lower limbs, both proximally and in the calves, whereas that occurring in people taking placebo tends to be more generalised throughout the body.³ The myalgia associated with vitamin D deficiency can also be generalised, so blood tests should include vitamin D as well as CK.

Probably the most common challenge is a patient with rather diffuse myalgia, present at rest but worsened by activity, who has no demonstrable weakness and a normal serum CK. In this situation, electromyography and muscle biopsy are very unlikely to provide an answer, but if undertaken—sometimes at the patient's insistence—may confuse matters further because they show 'minor changes of uncertain significance'. Clinicians should certainly consider electromyography and biopsy if the serum CK is clearly elevated, but even so, if myalgia is the sole feature, these tests are rarely productive. Nevertheless, many neuromuscular specialists have anecdotes about conditions such as myotonic dystrophy type 2, which can present with a 'fibromyalgia-like' syndrome in middle age,³³ although more recent studies have challenged the association.³⁴

Further research will possibly reveal a mechanism whereby statins may precipitate myalgia with persistence after withdrawal but as with myalgia in the general population, many cases remain unexplained.

STATINS IN THOSE WITH PRE-EXISTING MYOPATHY**Does a pre-existing myopathy increase the risk of developing a statin-related myopathy?**

The simple, and clinically relevant answer, is 'no'. Vladutiu and colleagues suggested an association between carrier status for McArdle's disease or carnitine palmitoyltransferase deficiency, or homozygosity for myoadenylate deaminase deficiency, with an increased risk of statin-induced muscle symptoms, including pain, fatigue, weakness and rhabdomyolysis.³⁵ However, numerous methodological concerns (especially patient self-reporting and most patients having no formal clinical assessments) greatly limit their conclusions, and no subsequent studies have confirmed such associations.

However, it would be naïve to ignore two truths. First, that many people with a neuromuscular disorder are understandably introspective about their condition and associated symptoms. Second, that there is a huge lay-press literature 'warning' of the dangers of statins (see comments about nocebo effect above). For these reasons, clinicians should take a precautionary approach to prescribing statins in these patients. This is summarised at the end of the following section

considering the reverse phenomenon—the possibility that statins exacerbate the pre-existing neuromuscular disorder.

Can statins exacerbate a pre-existing myopathy?

The answer is a very guarded ‘yes’. However, there is probably no situation where somebody with a pre-existing neuromuscular disorder should withhold statins if there is a clear clinical need for them. As discussed immediately above, it is essential to engage fully with the patient in discussing issues and to follow the precautionary approach outlined below.

There is little literature concerning statins exacerbating a pre-existing myopathy; considering the many millions of doses prescribed, this in itself suggests that there is not a major problem. Statins impair CoQ synthesis and there has been much speculation, but no certain proof, that this may be one of the mechanisms by which statins cause myopathy. In many mitochondrial cytopathies, there is respiratory chain function impairment, and statin-induced lowering of CoQ might in theory exacerbate the underlying disorder. Two rather limited case reports of patients with the mtDNA A3243G mutation suggested that statins might have precipitated features of MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) syndrome in one³⁶ and elevated serum CK in the other.³⁷ I am aware of verbal anecdotal reports of statins apparently exacerbating fatigue and weakness in other mitochondrial disorders, but once again the nocebo effect needs to be considered, and there is a complete lack of literature to suggest that this is a major issue.

There is a small literature suggesting that statins may precipitate or exacerbate myasthenia gravis; however, myasthenia symptoms are notoriously variable, with patients frequently making associations between exacerbation of symptoms and possible environmental triggers. The most recent review identified fewer than 20 cases in the world literature, noting also that as many as 60 000 people in the USA alone may have myasthenia—with millions of the population receiving statins³⁸—any risk therefore seems to be very small.

Precautionary prescribing

Statins can be used in those with a pre-existing neuromuscular disorder, with only a low risk of either statin-related myopathy or exacerbation of the underlying disorder. Although many of the anxieties relating to statins may be unfounded, they are extensively discussed in the lay literature, and it is imperative to have an appropriate discussion with the patient and record this in their notes. **Box 8** outlines a reasonable precautionary approach, and this should ensure that patients are not denied the potential benefits of statins and that any risks are minimal. It is always worth checking thyroid

Box 8 Prescribing statins in people with a pre-existing neuromuscular disorder

- ▶ Counsel the patient and record in notes
- ▶ Baseline serum creatine kinase (CK) (and check thyroid function)
- ▶ Start low-dose statin (eg, simvastatin 10 mg)
- ▶ Monitor
 - ▶ Clinical
 - ▶ Serum CK
 - ▶ Serum cholesterol
- ▶ Slowly increase the statin dose as required

function if not done recently, since hypothyroidism can cause hypercholesterolaemia and a raised serum CK. It also increases the risk of statin-induced problems including myalgia and rhabdomyolysis. On current evidence, there is little if any difference in risk of myotoxicity between the different statins, so use whatever is local policy, but start at a low dose, increase the dose as needed depending on the serum cholesterol and continue monitoring clinically and biochemically.

CONCLUSION

Statins are highly effective in lowering the serum cholesterol concentration. There are two major classes of adverse effects on muscle. First, through some uncertain metabolic effect, probably relating to downstream effects of the pathway being inhibited, patients may develop myalgia, typically affecting the proximal lower limb muscles. Rhabdomyolysis is a more extreme metabolic effect; it may relate to a very high therapeutic dose or to an effectively high dose caused by inhibition of statin metabolism (through the cytochrome p450 pathway) by another therapeutic agent, often an antimicrobial compound, cardiac drug or fibrate.

Second, statins may induce an immune response, with antibodies directed against the HMGCR enzyme, causing an immune-mediated necrotising myopathy. This may remit on stopping the statin, but more often persists and requires aggressive immunotherapy to induce remission.

Predisposing factors to the metabolic complications include an *SLCO1B1* polymorphism, greater age and numerous comorbidities. Symptoms resolve rapidly on stopping the statin.

Anti-HMGCR immune-mediated necrotising myopathy is strongly associated with HLA DRB 1*11:01, but there is no justification to screen patients before starting statins.

There is little evidence that statins exacerbate pre-existing neuromuscular disorders, with only a limited literature relating to mitochondrial disorders, metabolic disorders and myasthenia gravis. Patients with such disorders should certainly not be denied

Key points

- ▶ Statin-induced myalgia is relatively common but reversible on drug withdrawal; it usually resolves on reducing the dose or changing the statin.
- ▶ Statins are probably the the most common underlying cause of rhabdomyolysis, often precipitated by drug–drug interaction.
- ▶ Statin-induced immune-mediated necrotising myopathy clinically mimics ‘myositis’ and usually requires immunosuppressant drug treatment.

statins treatment, but clinicians should follow simple precautionary guidelines.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned. Externally peer reviewed. This paper was reviewed by Simon Hammans, Southampton, UK.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J* 2014;168:6–15.
- 2 Argov Z. Statins and the neuromuscular system: a neurologist's perspective. *Eur J Neurol* 2015;22:31–6.
- 3 Parker BA, Capizzi JA, Grimaldi AS, *et al.* Effect of statins on skeletal muscle function. *Circulation* 2013;127:96–103.
- 4 Collins R, Reith C, Emberson J, *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;388:2532–61.
- 5 Thompson PD, Taylor B. Safety and efficacy of statins. *The Lancet* 2017;389:1098–9.
- 6 Collins R, Armitage J, Baigent C, *et al.* Safety and efficacy of statins – Authors' reply. *The Lancet* 2017;389:1099–100.
- 7 Tobert JA, Newman CB. The nocebo effect in the context of statin intolerance. *J Clin Lipidol* 2016;10:739–47.
- 8 Hadjiphilippou S, Ray KK. PCSK9 inhibition and atherosclerotic cardiovascular disease prevention: does reality match the hype? *Heart* 2017;103:1670–9.
- 9 Noyes AM, Thompson PD. The effects of statins on exercise and physical activity. *J Clin Lipidol* 2017;11:1134–44.
- 10 Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Br J Clin Pharmacol* 2004;57:525–8.
- 11 Mas E, Mori TA. Coenzyme Q(10) and statin myalgia: what is the evidence? *Curr Atheroscler Rep* 2010;12:407–13.
- 12 Khayznikov M, Hemachandra K, Pandit R, *et al.* Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci* 2015;7:86–93.
- 13 Jetty V, Glueck CJ, Wang P, *et al.* Safety of 50,000–100,000 units of vitamin D3/week in vitamin D-Deficient, hypercholesterolemic patients with reversible statin intolerance. *N Am J Med Sci* 2016;8:156–62.
- 14 Riche KD, Arnall J, Rieser K, *et al.* Impact of vitamin D status on statin-induced myopathy. *J Clin Transl Endocrinol* 2016;6:56–9.
- 15 Mergenhagen K, Ott M, Heckman K, *et al.* Low vitamin D as a risk factor for the development of myalgia in patients taking high-dose simvastatin: a retrospective review. *Clin Ther* 2014;36:770–7.
- 16 Backes JM, Barnes BJ, Ruisinger JF, *et al.* A comparison of 25-hydroxyvitamin D serum levels among those with or without statin-associated myalgias. *Atherosclerosis* 2011;218:247–9.
- 17 Eisen A, Lev E, Iakobishvili Z, *et al.* Low plasma vitamin D levels and muscle-related adverse effects in statin users. *Isr Med Assoc J* 2014;16:42–5.
- 18 Hou Q, Li S, Li L, *et al.* Association Between SLCO1B1 Gene T521C Polymorphism and Statin-Related Myopathy Risk: A Meta-Analysis of Case-Control Studies. *Medicine* 2015;94:e1268.
- 19 Liu JE, Liu XY, Chen S, *et al.* SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case-control study. *Eur J Clin Pharmacol* 2017;73:1409–16.
- 20 Floyd JS, Brody JA, Tiniakou E, *et al.* Absence of anti-HMG-CoA reductase autoantibodies in severe self-limited statin-related myopathy. *Muscle Nerve* 2016;54:142–4.
- 21 Wiggins BS, Saseen JJ, Page RL, *et al.* Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American heart association. *Circulation* 2016;134:e468–e95.
- 22 Hylton Gravatt LA, Flurie RW, Lajthia E, *et al.* Clinical Guidance for Managing Statin and Antimicrobial Drug-Drug Interactions. *Curr Atheroscler Rep* 2017;19:46.
- 23 Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006;80:565–81.
- 24 Christopher-Stine L, Casciola-Rosen LA, Hong G, *et al.* A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. *Arthritis Rheum* 2010;62:2757–66.
- 25 Tiniakou E, Christopher-Stine L. Immune-mediated necrotizing myopathy associated with statins: history and recent developments. *Curr Opin Rheumatol* 2017;29:604–11.
- 26 Tiniakou E, Mammen AL. Necrotizing myopathy caused by central hypothyroidism. *Muscle Nerve* 2015;52:152–3.
- 27 Nazir S, Lohani S, Tachamo N, *et al.* Statin-Associated Autoimmune Myopathy: A Systematic Review of 100 Cases. *J Clin Rheumatol* 2017;23:149–54.
- 28 Karunaratne K, Amiras D, Pickering MC, *et al.* Autoimmune necrotising myopathy and HMGCR antibodies. *Pract Neurol* 2018;practneurol-2017-001848.
- 29 Mammen AL, Tiniakou E. Intravenous Immune Globulin for Statin-Triggered Autoimmune Myopathy. *N Engl J Med* 2015;373:1680–2.
- 30 Tiniakou E, Pinal-Fernandez I, Lloyd TE, *et al.* More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutarylcoenzyme A reductase-associated autoimmune myopathy. *Rheumatology* 2017;56:787–94.

- 31 Mammen AL, Gaudet D, Brisson D, *et al.* Increased frequency of DRB1*11:01 in anti-hydroxymethylglutaryl-coenzyme A reductase-associated autoimmune myopathy. *Arthritis Care Res* 2012;64:1233–7.
- 32 Allenbach Y, Keraen J, Bouvier AM, *et al.* High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. *Brain* 2016;139(Pt 8):2131–5.
- 33 Auvinen S, Suominen T, Hannonen P, *et al.* Myotonic dystrophy type 2 found in two of sixty-three persons diagnosed as having fibromyalgia. *Arthritis Rheum* 2008;58:3627–31.
- 34 van Vliet J, Verrips A, Tieleman AA, *et al.* No relevant excess prevalence of myotonic dystrophy type 2 in patients with suspected fibromyalgia syndrome. *Neuromuscul Disord* 2016;26:370–3.
- 35 Vladutiu GD, Simmons Z, Isackson PJ, *et al.* Genetic risk factors associated with lipid-lowering drug-induced myopathies. *Muscle Nerve* 2006;34:153–62.
- 36 Thomas JE, Lee N, Thompson PD. Statins provoking MELAS syndrome. A case report. *Eur Neurol* 2007;57:232–5.
- 37 Tay SK, Dimauro S, Pang AY, *et al.* Myotoxicity of lipid-lowering agents in a teenager with MELAS mutation. *Pediatr Neurol* 2008;39:426–8.
- 38 Khalid R, Ibad A, Thompson PD. Statins and Myasthenia Gravis. *Muscle Nerve* 2016;54:509.