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Statins seldom cause adverse reactions

PERSPECTIVES

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Statins seldom cause muscle side effects and are tolerated by the great majority of people. It is important to spend time, build trust, manage negative expectations and identify other causes of muscle problems than the use of statins.

Statins are cost-effective drugs that cause regression of atherosclerosis and lower the risk of cardiovascular disease, mainly by reducing the LDL cholesterol level (1, 2). Meta-analyses of randomised trials show that about 10 patients have to be treated with statins for five years to prevent one cardiovascular event in cases of established cardiovascular disease, while 20–50 at-risk patients have to be treated to achieve the same benefit (1).

Figures from the Norwegian Prescription Database show that more than one in ten persons in Norway is prescribed statins, mainly atorvastatin and simvastatin. However, only about 70 % of those who picked up prescriptions for statins for the first time in 2012 also picked up the drug at least once in 2013 and 2014. In other words, about one third stopped taking the drug (3). Muscle side effects are the principal reason for dose reduction or for patients discontinuing statins temporarily or permanently, with a subsequent increase in cardiovascular risk as a consequence (2). New data from randomised trials reveal no association between statins and muscle side effects in the great majority who report these effects.

Myopathy

Myopathy is characterised by proximal muscle pain, muscle weakness and a rise in the level of the muscle protein creatine kinase (CK) in the blood to more than 4–10 times the upper normal limit (2). Rhabdomyolysis is a severe form of myopathy in which creatine kinase rises to more than 40 times the upper normal limit, and is occasionally complicated by acute renal failure (2). The incidence of myopathy is estimated to be about 1 per 10 000 patients treated with statins per year, while rhabdomyolysis is estimated to affect 2–3 per 100 000 patients per year (4).

> ***«New data from randomised trials reveal no association between statins and muscle side effects in the great majority»***

There is limited understanding of the pathophysiology. High doses of statins, especially simvastatin 80 mg (which is no longer recommended), an Asian background, female sex, high age, low body mass index, diabetes and

concurrent use of interacting medicines, are predisposing factors (5). Myopathy normally resolves rapidly when statin treatment is discontinued (6). A rise in liver transaminase values is often observed concurrently with an increase in creatine kinase, but this is reversible and not associated with an increased risk of hepatic disease (6). Autoimmune myositis can be observed in rare cases, with inflammation and muscle necrosis which progresses despite the discontinuation of statins (7). These patients often benefit from immunosuppressant therapy (7).

Other muscle symptoms

Statin-associated muscle symptoms is a collective term for frequently occurring symptoms such as cramps, tenderness, stiffness, pain and weakness in muscles and joints coupled with reduced capacity for work and/or fatigue, with a normal or minimal increase in creatine kinase (2, 8). The incidence in observational and registry studies is 10–30 % higher in persons who use statins than in persons who do not (8). However, randomised controlled trials have not revealed significant differences in the incidence of muscle side effects (9, 10). In a meta-analysis of 26 double-blind, randomised trials with almost 60 000 participants, only a weak tendency to more muscle symptoms was found in statin users compared with those who received a placebo (12.6 % v. 12.4 %). There was no difference between the groups in the proportion with a rise in creatine kinase or the proportion who discontinued statins because of muscle problems (9). A similar result was found in another meta-analysis with five years of follow-up (10).

> ***«Some people experience adverse reactions from statins simply because they expect to»***

It has been speculated that the explanation for the discrepancy between the incidence of muscle problems in randomised trials and in observational studies may be that patients who have previously experienced adverse reactions or are at high risk of adverse reactions are excluded from randomised statin trials (9). The absence of a standardised definition of myalgia, run-in periods prior to trials, and underreporting of symptoms are other explanations that have been proposed (9).

Statin versus placebo

In order to make a closer study of muscle-related symptoms associated with statins, researchers have conducted several crossover trials in recent years in which participants undergo one or more double-blinded periods of treatment with both statin and placebo in random order (11–13).

In a Norwegian crossover trial conducted in 2016–2018, more than 2 000 myocardial infarction patients were screened (11). Around 10 % of potentially includable patients reported ongoing muscle side effects when treated with atorvastatin or had discontinued atorvastatin because of adverse reactions. There was no difference in the intensity of average muscle symptoms during the period with atorvastatin compared with the placebo period. Nor was there any correlation between muscle symptoms and measured levels of creatine kinase, alanine aminotransferase, potentially toxic statin metabolites or genetic variants (*CYP3A* and *SLCO1B1*) that are assumed to be associated with adverse reactions to statins (11). At the end of the trial, all the patients received information about their own results, and about 90 % tolerated either atorvastatin or rosuvastatin with a subsequent expected reduction in LDL cholesterol after 13 months of follow-up (14).

Two British trials have shown similar results (12, 13). One trial estimated that 90 % of the symptoms reported during statin therapy were a result of taking the tablet – whether it contained a statin or not (13). Even among carefully selected and supposedly statin-intolerant patients who were recruited to test the effect of proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors, almost 80 % tolerated blinded treatment with 20 mg/day atorvastatin (15).

The nocebo effect

The nocebo effect implies a negative expectation and may lead some individuals to experience statin side effects quite simply because they expect them. A Danish study demonstrated that negative media coverage of statins was associated with early discontinuation and a subsequent increase in the incidence of cardiovascular disease, while positive media coverage had the opposite effect (16).

The nocebo effect has been documented in several trials (13, 17). A physiological substrate for this effect was detected recently (18). In a relevant experiment, a negative expectation was introduced that participants who used an 'expensive and effective cream' would experience more discomfort than those who used a 'cheap' cream. Participants who used the expensive cream reported considerably more problems, although the content was identical. Functional MR imaging during the experiment demonstrated differences in activity between the groups in areas of the brain involved in pain management (18).

Practical management

We believe there are grounds for maintaining that statins are not the cause of muscle problems among the majority who report pain of this nature in clinical practice (11–15). Health personnel are recommended to allocate sufficient time with the individual patient to build a good relationship of trust (2, 8, 19). It is

also important to explain to patients that statins are administered not merely to reduce a number, but that they actually cause regression of atherosclerosis and protect the individual from illness and death.

> ***«A thorough clinical history to show the relationship between intake of statins and symptoms, along with examination of alternative explanations for muscle symptoms, are of key importance»***

Patients' negative expectations regarding statin therapy should be managed, preferably in connection with prescription, by providing information about the beneficial preventive effect on cardiovascular disease, the low risk of adverse reactions and the good tolerability, which have now been documented in robust scientific studies (2, 8, 19). Many patients treated with statins are elderly, and there are several other possible reasons for their muscle problems. A thorough clinical history to show the relationship between intake of statins and symptoms, coupled with examination of alternative explanations for the muscle symptoms, such as musculoskeletal disorders or rheumatic disease, is therefore of key importance. (8, 14, 19). Breaks in drug therapy may help, and if the symptoms do *not* disappear within four weeks without statins, they very likely have another cause. A few very intolerant patients, often thin, elderly women, should be started on the lowest dose of atorvastatin or rosuvastatin, which because of their long half-life can be administered 2–3 times a week, with slow upward titration to the highest tolerable dose (2, 8). If this strategy is applied, our experience is that the great majority tolerate a statin.

Myopathy and rhabdomyolysis with a rise in creatine kinase occur very rarely. These conditions are reversible with few exceptions if the statin is discontinued for 4–6 weeks, and many will tolerate a statin from a different class if they are started on a low dose and gradually titrated up (6, 8). It is recommended that for this group the creatine kinase level should be monitored for the first few months after a change of medication. Investigating whether the patient uses interacting medicines is also recommended (2, 8). Some patients may have a high creatine kinase level without symptoms. This is often due to physical activity. In these cases it is important to tell the patient not to exercise in the week before a new blood test.

Ezetimibe inhibits the absorption of cholesterol from the bowel, is well tolerated and reduces the LDL cholesterol level achieved by statin therapy by a further 10–15 % (2). Combination therapy is therefore important and recommended (2) in attempts to attain the recommended LDL cholesterol levels.

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