Side effects during cholesterol management

Is statin therapy always the cause?

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Statin drugs are consumed by very large numbers of people. Side effects are not frequent, but they are well documented and include statin-induced myalgia. However, not every new symptom on such treatment is genuinely attributable to statin therapy and investigation of other causes should be undertaken when symptoms persist after statin cessation.

Around one in six Australian adults are taking a statin drug for cholesterol control and cardiovascular disease prevention.[1] Given these very large numbers, the incidence of adverse events is acceptably low. However, every medical practitioner has witnessed a small proportion of patients with side effects when using statins. These include muscle symptoms, new-onset diabetes, liver dysfunction, drug-drug interactions and central nervous system symptoms.[2] Fear-mongering in the lay media portrays adverse events in an unbalanced manner, highlighting side effects while ignoring positive benefits. Many prescribers and indeed patients seek to avoid any statin therapy because of the presence of or concern for statin-associated side effects.

This article describes the clinical history of a man experiencing adverse events while using statins, but with an unexpected outcome.

Case scenario

CG, a 40-year-old man, attended his GP for a physical examination and some routine blood tests, which arose from a life insurance proposal. He was smoking 25 cigarettes/day (a 20 pack-year history), was not significantly overweight (body mass index 25.1 kg/m^2) and his blood pressure was acceptable at 128/78 mmHg (mean of several measurements). Blood tests covering a full blood count, electrolytes, creatinine, glucose and muscle enzyme levels, inflammatory markers and thyroid and liver function were within normal limits. His lipid profile was highly adverse: total cholesterol, 8.0 mmol/L; triglyceride, 2.1 mmol/L; HDL-C, 0.9 mmol/L and LDL-C, 6.1 mmol/L.

His father was known to manifest 'high cholesterol' and presented with an acute coronary syndrome six months previously, at age 64 years. His GP made a likely diagnosis of familial hypercholesterolaemia. Lipid tests were repeated a week later with similar results, and CG was given lifestyle and dietary advice. Atorvastatin was commenced several months later because of a persisting elevation in LDL-C level.

Nine years later, CG continues to smoke despite counselling from his GP. For cholesterol control, he is managed with a combination of diet, atorvastatin at 40 mg daily and ezetimibe 10 mg daily. His lipid profile has improved considerably: total cholesterol, 4.2 mmol/L; triglyceride, 1.9 mmol/L; HDL-C, 1.0 mmol/L; and LDL-C, 2.3 mmol/L.

CG now reports a mild degree of myalgia in his arms and legs, plus mild arthralgia in his hands and wrists, and his GP diagnoses a statin-induced muscle problem. The level of muscle enzyme creatine kinase (CK) is within the reference range at 130 U/L. Other blood test results are within normal limits. After a four-week washout period, CG is switched from atorvastatin to rosuvastatin 20 mg daily, later increased to 40 mg daily. The muscle and joint symptoms persist, but CG describes them as quite mild and tolerable.

One year later, CG presents with an acute coronary syndrome and is diagnosed with two-vessel coronary disease and successfully stented. He quits smoking, begins additional cardiac medications prescribed by his cardiologist and continues lipid therapy (rosuvastatin 40 mg plus ezetimibe 10 mg daily). Over the next six months his muscle and joint symptoms gradually become more severe and statin therapy is suspended. Within a few days of cessation, his myalgia improves markedly but arthralgia and stiffness in his wrists remain unchanged. On resuming rosuvastatin, myalgia returns and statin therapy is again suspended.

MedicineToday 2021; 22(12): 48-49

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He is seen by a rheumatologist who notes swelling and some limitation of movement in both wrists, plus swelling in metacarpophalangeal and proximal interphalangeal joints in one hand. The rheumatologist confirms a diagnosis of seropositive rheumatoid arthritis, based on additional blood tests: erythrocyte sedimentation rate, 56 mm/h; C-reactive protein, 45 mg/L (reference <5.1 mg/L); rheumatoid factor, 66 IU/mL (reference <14 IU/mL); cyclic citrullinated peptide antibodies, >200 RU/mL (reference <4 RU/mL); and negative antinuclear antibody titre, 1:80.

What is the diagnosis?

A recent Medline search for 'statins and myopathy' identified almost 3,000 literature reports over the past 30 years. It is likely that CG has developed a statin-associated muscle problem, one without elevated CK levels when tested at 49 years of age. It is curious that more severe symptoms only developed after many years on treatment.

Although highly elevated CK readings (>1000 U/L) may be indicative of a serious underlying myopathic process, 80 to 90% of patients with a mild degree of statin-associated myalgia have no significant change in CK level.[2] Improvement in CG's myalgia on stopping statin therapy and reappearance of similar symptoms on challenge with statins further supports the diagnosis of a statin-induced problem. That said, in a placebo-controlled trial in patients reporting previous statin-associated muscle symptoms, cessation of statin and then double-blind challenge with statin did not uniformly lead to a return of symptoms.[3] This suggests that some patients can later return to statin therapy, but perhaps at a lower dose.

The mechanisms underlying statin-associated muscle problems are poorly understood, and not simply due to a reduction in tissue coenzyme Q10 levels. Hypothyroidism- and vitamin D deficiency-associated myopathy need to be excluded. There is a very rare form of statin-associated myopathy having an autoimmune basis. Patients with this form of myopathy have antibodies to hydroxymethylglutaryl-CoA reductase and marked elevation in CK level, the latter continuing even after statin cessation.[4]

In the setting of cardiac disease and polypharmacy, there is a potential for drug-drug interaction between statin drugs that are metabolised via the 3A4 pathway in the liver, notably simvastatin and atorvastatin, and other drug classes including the calcium channel blocker diltiazem and the antiarrhythmic drug amiodarone. These interactions can lead to an increased risk of statin toxicity.

It is not unusual for patients with statin-associated muscle symptoms to also report arthralgia, and the diagnosis here can be confusing. CG's presentation is unusual in that he developed a second clinical problem, rheumatoid arthritis. Interestingly, no increase in inflammatory markers was noted during the early years of his therapy.

Although rheumatoid arthritis is an autoimmune inflammatory disorder associated with increased risk of cardiovascular disease, there is no evidence that statins induce the onset of rheumatoid arthritis.[5] In fact, statins have a mild anti-inflammatory action. This patient reported improvement in myalgia on statin cessation, yet his joint symptoms persisted, ultimately leading to the second diagnosis.

How should this patient be managed?

Despite some improvement in cholesterol control, CG still developed significant coronary artery disease. Possible reasons for this might be that:

- his lipid therapy was initiated at a mature age
- statins cannot abolish all future coronary disease
- an additional risk factor such as elevated lipoprotein(a) level was present
- he continued with cigarette smoking.

He will need ongoing therapy for his continuing cholesterol elevation as therapy with ezetimibe alone will not suffice. He also remains highly symptomatic with rheumatoid arthritis and therapy for this cannot be delayed.

CG is commenced immediately on a standard regimen for rheumatoid arthritis, initially prednisone and methotrexate. Within one week his joint symptoms have shown marked improvement and disease-modifying therapy is to follow.

Further statin therapy is best avoided. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is an appropriate choice for cholesterol control, although clinical experience of using PCSK9 inhibitors in patients with rheumatoid arthritis is limited.[6] For that reason CG is started on alirocumab at a low dose of 75 mg self-injected subcutaneously every two weeks, leaving open the possibility of an increase to the standard 150 mg dose if he does not achieve an LDL-C level of below 1.8 mmol/L.[6] Four weeks into treatment he reports no myalgic side effects and excellent improvement in joint symptoms. This lipid therapy will likely be continued on a permanent basis, with regular clinical review.

Conclusion

Statin therapy may sometimes induce myalgia, often unaccompanied by major change in muscle enzyme levels. Statin cessation is usually accompanied by complete resolution of muscle symptoms, often within a few days. Persistence of myalgia or other symptoms many weeks after statin cessation should raise the possibility that another musculoskeletal or joint condition is present. MT

References

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COMPETING INTERESTS: Associate Professor Simons has previously received clinical trial or consultancy fees from manufacturers of lipid-modifying drugs.