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Reinitiation of Statins After Statin-Associated Musculoskeletal Symptoms

A Patient-Centered Approach

Juan P. Brito, MD; Victor M. Montori, MD, MSc

A 58-year-old man receives primary care for obesity, hypertension, smoking, and dyslipidemia. He used atorvastatin until a few months ago but stopped because of muscle discomfort with activity, night cramps, and tendon soreness. He comes today to discuss treatment for his dyslipidemia.

Coronary artery disease is a leading cause of premature morbidity and mortality worldwide.[1] Although highly prevalent, cardiovascular mortality has decreased over the last few decades in high-income countries.[2] This success has resulted from improvements in public health, control of cardiovascular risk factors, and increased use of evidence-based therapies to prevent and treat coronary disease.[3]

The use of 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors, or statins, stands tall among evidence-based therapies that are able to reduce cardiovascular risk. The ability of statins to reduce cholesterol blood levels and to reduce cardiovascular risk is well established. The use of adherent statin can reduce coronary risk by 25%, with greater reductions possible with higher doses.[4] Worldwide, practice guidelines reflect experts' confidence in this evidence of efficacy, recommending statins to at-risk patients, making statins one of the most prescribed medication classes in modern medicine.[5] This confidence contrasts with the limited or unknown efficacy in reducing coronary risk of other available and commonly used lipid-lowering agents (eg, fibrates, niacin, fish oil, ezetamibe).[6–9]

The efficacy of statins, however, is limited in part by statin discontinuation. In some cohorts, half of all patients, even those at highest risk of coronary events, discontinue statin therapy within 2 years of their prescription.[10,11] Much of this discontinuation may be attributed to the complex phenomenon of patient nonadherence. Another explanation is the development of side effects in general and of musculoskeletal complains in particular.

Estimates of the incidence of these musculoskeletal symptoms attributed to statins vary according to study design, statin studies, and definitions used. Randomized clinical trials with narrow exclusion criteria estimate the incidence of these complaints to be between 1% and 5%.[12] Large observational studies estimate their incidence at ≈10%.[13,14] A recent prospective study in clinical practice found these complaints to be as frequent as 15%.[15] Taken together, clinicians will have to address musculoskeletal complaints linked to statins in 1 of every 10 patients to whom they prescribe statins. The key challenge for the clinician is to find, when possible, a way to preserve the cardiovascular benefits of statins in patients experiencing musculoskeletal side effects attributed to statins.

Here, we present an approach to support clinicians and patients in making the decision to reinitiate statins. We offer a practical definition of the problem, identify risk factors for it, and formulate a model for engaging patients in making treatment decisions about statin reinitiation.

Need for a Practical Definition

Several expert societies have offered criteria for the diagnosis of musculoskeletal symptoms attributed to statins. The American College of Cardiology, American Heart Association, and the National Heart, Lung and Blood Institute of the National Institutes of Health define the presence of any muscle symptom without elevation of creatine kinase (CK) as myalgia and with CK elevation as myositis.[16] The attribution of musculoskeletal symptoms to statins is difficult, and most complaints are not associated with abnormalities of CK, an imperfect marker of muscle damage.[17] Therefore, these definitions relate symptoms to an unreliable marker of muscle damage and ignore a significant proportion of patients who present with tendinopathy[14] rather than with myalgias.

Statin-associated musculoskeletal syndrome (SAMS) comprises musculoskeletal symptoms or signs (muscle or tendon discomfort, pain, or impaired function) that develop while the patient is taking statins, decrease the health-related quality of life of the patient, and resolve after statin discontinuation. We have not been able to identify data to support the subclassification of SAMS according to whether CK levels are elevated at the time of diagnosis. In the absence of this evidence, we suggest managing all forms of SAMS, whether associated with CK elevations or not, similarly.

Rhabdomyolysis is a rare (1 in 20 000 patients) and severe form of SAMS diagnosed on the basis of its clinical presentation supported by laboratory abnormalities suggestive of muscle breakdown and acute renal failure. We concur with existing guidelines that recommend discontinuation of statins in patients who have experienced rhabdomyolysis[16] and do not offer additional guidance here.

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Assessment of Risk Factors for SAMS

Before considering reinitiation of statin therapy, patients and their clinicians need to consider risk factors for SAMS and identify which ones have contributed to the presentation of the patient and which of these can and cannot be modified.

Modifiable Risk Factors for SAMS

A systematic review of 27 548 patients found a greater incidence of SAMS (odds ratio=9.97; 95% confidence interval, 1.28–77.92) in patients receiving intensive-dose statin therapy compared with standard-dose therapy.[18] Likewise, more patients experience myopathy (defined as unexplained muscle symptoms with persistent CK elevation of >10 times the upper limit of normal) with 80 mg than with 20 mg of simvastatin (53 versus 2; relative risk=26.5; 95% confidence interval, 6.4–157) in the 12 064-patient SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial.[19] After evaluating these data, the US Food and Drug Administration limited the use of simvastatin (80 mg) because of increased risk of muscle damage.

SAMS may also differ depending of the type of statin. The Prediction of Muscular Risk in Observational condition (PRIMO) study, including 7924 patients receiving statins in France, reported different rates of SAMS with fluvastatin 40 mg (5%), pravastatin 40 mg (11%), and simvastatin 40 to 80 mg (18%).[13] A meta-analysis including 71 108 people, 36 062 on statins and 35 406 on placebo, reported the greatest risk of SAMS with atorvastatin and the least risk with fluvastatin.[20] Different rates have been attributed to pharmacological differences between statins. For instance, rosuvastatin and pravastatin are less lipophilic than other statins and theoretically have a lower chance of affecting muscle cells directly.[21] For this reason, patients with low body mass index may be more likely to develop SAMS with these agents. These 2 drugs are also primarily metabolized by cytochrome 2C9, a site with fewer drug–drug interactions than cytochrome 3A4 that metabolizes simvastatin, lovastatin, and atorvastatin.[22] Indeed, drug–drug interactions may play a role in some cases of SAMS. Drugs inhibiting glucuronidation, such as gemfibrozil, or drugs affecting cytochrome 3A4 activity, eg, amiodarone, protease inhibitors, niacin, azole antifungals, macrolides, and nondyhydropyridine calcium channel blockers, affect the clearance and increase the blood levels of statins.[16]

In addition to drug selection and dose and drug–drug interactions, other modifiable risk factors for SAMS include drug–habit interactions (eg, use of >1 L/d of grapefruit juice, heavy alcohol use, heavy exercise) or drug–disease interactions (eg, hypothyroidism).[16,23,24]

Immutable Risk Factors

Other important risk factors for SAMS are age >65 years, family or personal history of SAMS, unexplained muscle cramps, and rare hereditary metabolic muscle diseases.[23,24] Likewise, recent studies also suggest a genetic contribution to SAMS. A genome-wide study in patients treated with simvastatin found that a polymorphism in the gene *SLCO1B1*, which encodes an organic anion–transporting polypeptide that facilitates transportation of statins into hepatocytes, was associated with SAMS.[25] However, this association has not held for other statins.[26]

Patient-Centered Approach

The issues involved in restarting statins include technical considerations and patient goals and preferences. Clinicians can work on the technical aspects, eg, addressing modifiable risk factors, but need to engage patients in shared decision making to take into account their goals and preferences. This process involves sharing pertinent information about the options and their relative merits, considering their pros and cons in light of patient values, and making a consensual decision with detailed plans for its execution.

Establishing the Diagnosis of SAMS

The clinician needs to consider whether the patient complaint represents SAMS or an alternative diagnosis. After excluding alternative diagnoses, clinicians should determine the extent to which the musculoskeletal symptoms experienced affect the quality of life of the patient. This would include disruptions or impairments during work, recreation, or sleep attributed to SAMS. Our patient reports feeling bothered importantly by exercise-induced myalgia, night cramps, and tendon soreness, symptoms that satisfy criteria for SAMS and for which there appears to be no other explanation (Figure).

Assessment of Cardiovascular Risk

To frame the discussion, it is important to determine what the patient risk of cardiovascular events is. Using existing calculators (eg, Framingham Risk Score), clinicians can estimate this risk, which for our patient is 22% at 10 years.

Assess and Consider the Potential Benefit of Evidence-Based Therapies

Clinicians and patients should then review the potential value of statins for this patient. This discussion should start by considering everything else the patient is doing at this time to reduce his or her cardiovascular risk.

Our patient, unfortunately, is sedentary and continues to smoke. He is not taking aspirin, and his blood pressure is being treated with a poorly implemented Dietary Approaches to Stop Hypertension diet. In this context, standard-dose statins (eg, 40 mg of pravastatin) can reduce his risk by 25%, from 22% to 17%.

Using state-of-the-art risk communication tools (eg, http://statindecisionaid.mayoclinic.org), clinicians can explain to patients what this risk reduction means, so that patients can consider whether the pursuit of this reduction is worth the work and potential suffering associated with therapeutic trials of other statins. Patients at very low cardiovascular risk will likely opt to focus their health efforts in areas other than lowering-lipid fractions and cardiovascular risk. Clinicians must reassure these patients because some (eg, patients with high low-density lipoprotein cholesterol levels as their only risk factors, low-cardiovascular-risk patients with diabetes

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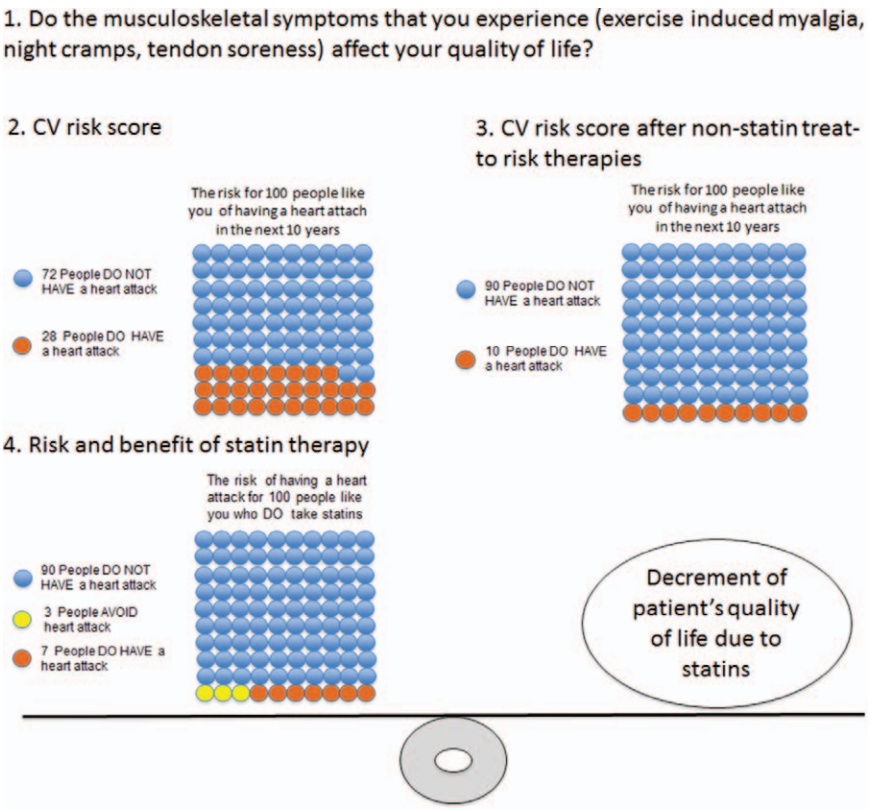

Figure. Stepwise approach to engage patients with statin-associated musculoskeletal syndrome in shared decision making. CV indicates cardiovascular.

mellitus) might have been mistakenly informed that they were at high risk for cardiovascular events. Patients at high cardiovascular risk who value the risk reduction afforded by statins and are willing to run the risk of SAMS to find the right statin will proceed with the next step. Patients at high risk who are less willing to experience SAMS (eg, a construction worker, a marathon runner, a patient with moderate SAMS) may instead choose to focus on other ways to reduce cardiovascular risk.

For our patient, this might involve improving physical activity, quitting smoking, and starting aspirin. Taken together, these therapies may reduce his risk by >50%,[27] taking his 10-year risk from 22% to ≈10% without using statins. Of course, if statins were to be considered after all these interventions are in place, their benefit to the patient would be smaller in absolute terms: a reduction in 10-year coronary risk of 25%, from 10% to 7.5%.

Restarting Statins

After considering other risk-reducing interventions, there will be patients who value the benefits of statins on cardiovascular risk and who remain interested in trying other statins in search of one they can tolerate.

Modalities for Reinitiation of Statin Therapy

If the diagnosis of SAMS was correct and there were no risk factors to modify, SAMS will likely recur after the same statin is resumed at the same dose.[28] Two modifications may reduce the risk of recurrence of SAMS: switching to another statin and decreasing the dose. To the best of our knowledge, the statins with the lowest rates of SAMS include pravastatin, fluvastatin, and rosuvastatin. Using a low dose (either by reducing the daily dose or by reducing the frequency of administration) of any of these could achieve the goal of SAMS-free adherence to statins. There is scant direct evidence to reliably guide the treatment of SAMS patients with statins. Two very small observational studies enrolling patients with history of SAMS suggest that choosing a low-risk statin and reducing the dose could improve the likelihood of SAMS-free adherence to statins in high-risk patients. In the first study, 51 patients received rosuvastatin 5 to 10 mg every 2 days with 20% recurrence of SAMS at 4.6 months.[29] In the second study, 61 patients received 5 to 10 mg daily with recurrence of SAMS in 1 patient at 44 weeks.[30] Existing evidence from randomized trials[31] and observational studies[32] does not support the use of concomitant agents, such as coenzyme Q_{10}, to prevent SAMS.

Clinical Uncertainty

When a patient is able to tolerate a statin at a given dose, the clinician may find that this dose is lower than that tested in clinical trials, thus creating some uncertainty as to whether the patient is indeed receiving adequate cardiovascular risk reduction. The lower the dose is compared with the clinical trial doses (eg, pravastatin 20–40 mg), the greater this uncertainty will be.[8] It is important here to remind us that the Heart Protection Study, the only randomized trial to explore this relationship without confounding, found no correlation between reduction in cardiovascular risk and magnitude

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of lowering of low-density lipoprotein cholesterol levels.[33] Furthermore, a focus on low-density lipoprotein targets rather than on cardiovascular risk will lead clinicians to offer therapies for which reliable evidence of cardiovascular risk reduction is not available (eg, ezetimibe) or indicates inefficacy (eg, fibrates, niacin, fish oil). Thus, clinical trials that suggest that less frequent dosing schemes result in comparable lipid profiles (eg, rosuvastatin 80 mg weekly versus atorvastatin 10 mg daily) only indirectly apply to the care of patients with SAMS.

New statins, such as pitavastatin available in the United States since 2009, have a different pharmacological profile,[34] which may be associated with a lower risk of SAMS, but not enough evidence exists to substantiate this claim. Indeed, SAMS as a syndrome may have multiple causal pathways in which exposure to a statin and susceptibility to SAMS may be necessary but not sufficient to result in SAMS. Much work is needed to fully understand the mechanisms that result and predict SAMS. The goal of this research would be to increase the likelihood that patients interested in reducing their cardiovascular risk will be offered an effective program with statins they can tolerate, without SAMS.

Conclusions

Statins aimed at improving the cardiovascular risk of our patient caused musculoskeletal side effects that reduced the quality of life of our patient and required statin discontinuation for resolution. Instead of taking a purely technical approach, we suggest that clinicians caring for patients with SAMS engage them in a dialog about the promised quantified benefits of statins in light of their potential to cause SAMS. Patients should recognize there are other interventions also capable of reducing their cardiovascular risk that they may have already implemented or may be available to them to use instead of statins. For patients who value the risk reduction with statins, clinicians should prescribe therapeutic trials with statins associated with low risk of SAMS and administered at lower doses or frequency. A close partnership with the patient may lead to a greater proportion of patients who are able to achieve their goals with therapies that do more good than harm.

Disclosures

None.

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