Statin Intolerance
Some Practical Hints

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KEYWORDS

• Adverse effects • Cardiovascular disease • Statins • Statin-associated muscle symptoms • Therapy

KEY POINTS

- Statin intolerance is a worldwide problem concerning the inability to tolerate a dose of statin required to sufficiently reduce cardiovascular risk.
- Muscle symptoms are the most common statin-associated adverse effects.
- New therapies with the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and bempedoic acid might be an effective response.

DEFINITION AND PREVALENCE

Statin intolerance is the inability to tolerate a dose of statin required to sufficiently reduce cardiovascular (CV) risk.[1] This limits the effective treatment of patients at risk of, or with, CV disease. Statin intolerance refers not only to the lack of statin treatment because of clinical or biochemical symptoms (so-called complete intolerance) but also to the treatment with insufficiently high statin doses or with insufficiently potent statins in relation to the CV risk level.[1,2]

Statin intolerance is a worldwide problem but interest in this phenomenon was intensified with the appearance of the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor studies in 2009.[3] Since 1994 and the Scandinavian Simvastatin Survival Study (4S) trial, in most of the available statin trials individuals with statin-associated adverse effects (SAAE) were excluded and therefore they did not show differences in drug safety between the statin and placebo groups, or between low/moderate and intense statin therapy.[2] The data on statin intolerance patients came from epidemiologic and observational studies, and the authors suggested that usually 15% to 20% of all patients on statin might suffer from different SAAE.[4]

The European Society of Cardiology/European Atherosclerosis Society consensus suggested that 29% of all patients treated with statins might present with statin-associated muscle symptoms (SAMS), but this number seems to be overestimated.[5] However, it is worth emphasizing that with the five-step approach (four diagnostic steps + therapy) for patients with statin intolerance, after excluding all conditions and risk factors that might increase this risk, and after introducing different methods of management (dose reduction, change of statin formulation, alternate-day therapy, combination therapy) more than 90% of these patients might be treated with statins and complete statin intolerance concerns only less than 5% of

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subjects (usually 1%–3%).[6] The principal approach should be to try not to discontinue statin therapy. This is a real challenge for lipidologists and those taking care of patients with dyslipidemia. Not discontinuing treatment is especially important for those with a high and very high CV risk. Statin discontinuation, which might concern even 50% to 60% of patients on statins after 2 years, is one reason why these patients often do not achieve their recommended goals of therapy (**Box 1**).[7–9]

SYMPTOMS AND CAUSALITY

SAMS are the most common adverse effects observed in patients on statins.[5] They might range from muscle weakness, muscle aches, soreness, stiffness, tenderness, and muscle cramps (but not nocturnal cramping; not necessarily with creatine kinase [CK] increase) to muscle myositis (with CK increase) and rhabdomyolysis (very rare at 1.6 per 100,000 patient-years), which is usually associated with genetic predisposition or other risk factors present during statin therapy (eg, kidney or liver disease, extensive exercise, or concomitant medication).[10,11]

It needs to be emphasized that one should always ask patients about the tolerability of muscle symptoms. If patients can tolerate the symptoms (with lack or slight CK increase) one should continue the treatment because the symptoms may be temporary and resolve after 2 to 4 weeks.[2] However, close follow-up should be maintained in case the symptoms and biochemical changes are progressive. It is important that patients should be fully aware about all the benefits of statin therapy and the CV risk increase caused by statin discontinuation or not taking a suitable statin dose.[8,9] Unfortunately, most patients usually know much more about SAAEs than the benefits associated with statin therapy. According to available data, there is several times more information on the Internet regarding side effects than on the benefits of statin use.[12] Because of this there are more and more patients with so-called nocebo effect, which is defined (despite completely different original definition of this phenomenon) as the appearance of statin-related side effects caused by patients' knowledge (eg, from media, Internet) and expectations and not by statin therapy.[1] The first strong data on the existence of this phenomenon are based on the recent subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) trial. In the nonrandomized phase there was a 41% significant increase of the rate of SAMS in patients treated with atorvastatin in comparison with the blinded phase, where there was no significant difference between groups.[13]

SAMS, statin-related new-onset diabetes, and alanine aminotransferase (ALT) elevation are the only side effects with confirmed causality.[1,2] There are also several other possible side effects after statin therapy, including highly debatable neurocognitive disorders[14] or erectile dysfunction[2] or sleep disorders, for which the causality has not been confirmed so far; there are also data that suggest a lack of such associations.[15]

From the clinical point of view it is important to clearly present the current recommendations on the association between statin therapy and liver diseases. First of all it is crucial to remember that ALT elevation greater than three times the upper limit of normal (ULN) occurs in less than 0.5% for moderate-dose statins and rosuvastatin at all doses, and about 1% for 80 mg of atorvastatin or simvastatin (usually <3% all together),[2] and usually returns to normal after a dose reduction without the need for statin discontinuation; in most cases it is possible to return to the initial doses of statins after 2 to 4 weeks.[2,10] Because of this most of the current recommendations suggest ALT measurement only before statin therapy and thereafter in case of side effects occurrence (without necessity of regular monitoring).[2,16,17] Finally, the risk of statin-related serious liver disease is 1 per 1,000,000 with the number needed to harm at 1 million. In comparison, use of statins prevents about 33% of major CV disease events when compared with placebo; the number needed to treat is 3. Unfortunately the percentage of patients who fail to receive statins because of fear of hepatotoxicity ranges between 10% and 30%.[2,18] Furthermore, available studies indicate that statin therapy should be continued and benefits are achieved in all patients with chronic liver diseases, and therapy should be stopped only in case of acute conditions.[2] The available data suggest that even in patients with hepatitis B and C viruses, although not in acute and active forms of the disease, statins significant decrease the risk of hepatocellular carcinoma (by <30%) and reduce in the incidence of hepatitis C virus in the blood by inhibiting its replication.[2,19] They might also be beneficial in patients with

Box 1
Practical hints on definition and prevalence of statin intolerance

- More than 90% of patients with statin intolerance might be treated with statins and complete statin intolerance only concerns less than 5% of subjects.
- The principal approach to patients with statin intolerance should be to try not to discontinue statin therapy.