Abstract

The efficacy and safety of statin therapy is well established. However, despite their favorable profile, muscle symptoms reported with statin use limit their use, impacting adherence and cardiovascular benefits of this therapy. It is important that clinicians are cautious before attributing muscle symptoms to statin therapy, without further investigation of their cause. Moreover, this is complicated by the lack of internationally agreed clinical definitions of statins-induced myopathy and diagnostic tools.

Recently, the European Atherosclerosis Society (EAS) Consensus Panel has circumvented the lack of consensus regarding the causality of statins with muscle symptoms by the use of the term Statin-Associated Muscle Symptoms, SAMS thus providing an accessible resource for the diagnosis, assessment and management of SAMS, as well as an update on current thinking about the aetiology of statin myopathy.

Understanding and clearly defining is critical for optimal treatment. Therefore, the management of SAMS is key in the effective treatment of patients with CardioVascular Disease (CVD), through achievement of maximum-tolerated statin dosing and other practical aspects. Combination therapy with ezetimibe and the addition of PCSK9 inhibitors in high-risk patients with elevated LDL-C is supported by a pharmacological and clinical evidence and is the logical approach to maintain patients on a statin therapy with the final aim to optimize the cardiovascular benefits of this treatment.

Statins (3-hydroxy-3-methylglutaryl Coenzyme A reductase [HMG-CoA] inhibitors) are the first line treatments for lipid management 1. The efficacy of these agents to reduce cardiovascular risk as related to the decrease in Low-
Density Lipoprotein Cholesterol (LDL-C) is well established. The available evidence spanning from Randomized Clinical Trials (RCT) to pharmacoepidemiology and clinical practice also shows that statins are safe and well tolerated. Despite this favorable profile, muscle symptoms reported with statin use can be problematic in the clinic, impacting treatment adherence and, in turn, the cardiovascular benefits of this pharmacotherapy.

RCT have shown that statin treatment is associated with a very rare serious myopathy with marked Creatine Kinase (CK) elevation, but have failed to delineate an association between statin therapy and milder muscle symptoms. Important caveats in reviewing safety data from clinical trials, however, are that many of the patients excluded from trials receive these agents in clinical practice and that patients in clinical trials differ from those seen in general practice in that the former are generally better informed and monitored and perhaps more compliant. For example, clinical trials protocols often exclude patients who may be more prone to myopathy, such as the elderly or who may have abnormal liver test results at baseline, and assumptions about safety may be overestimated. Therefore, the results in volunteer study participants who were monitored by lipid researchers may underestimate the incidence of myopathy when statins are used in unselected populations monitored with less precision. Despite this, clinicians commonly experience patients complaining of muscle symptoms on statin therapy in their routine practice, and acknowledge that this issue requires proper consideration. On the other hand, reports of observational studies that lack a placebo control, combined with the influence of the media on patients’ perception of statin side effects, can lead to an overestimation of the prevalence of such adverse effects. Furthermore, in an uncontrolled setting, a nocebo effect is also plausible, arising from mere expectations of harm from a drug, placebo or other therapeutic intervention. The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) Study Group recently evaluated the incidence of four different types of adverse events with statin therapy, including muscle-related symptoms, during both the blinded, placebo-controlled trial and its open-label extension study. The findings indicate that a nocebo effect may explain the higher incidence of statin induced myopathy in observational studies versus RCTs. In the light of above, it is important that clinicians are cautious before attributing muscle symptoms to statin therapy, without further investigation of their cause. Moreover, this is complicated by the lack of internationally agreed clinical definitions of statins-induced myopathy and diagnostic tools. Understanding and clearly defining is critical for optimal treatment. Several guidelines and clinical studies have defined statin intolerance, but this is not specific for SAMS and a unified widely accepted definition is lacking.

**Statin-Associated Muscle Symptoms (SAMS)**

The European Atherosclerosis Society (EAS) Consensus Panel has circumvented the lack of consensus regarding the causality of statins with muscle symptoms by the use of the term Statin-Associated Muscle Symptoms, SAMS. Definitions of SAMS have been proposed by the EAS Consensus Panel.
**Tabella I - Statin intolerance definitions from guidelines and trials.**

<table>
<thead>
<tr>
<th>Guideline/RCT</th>
<th>Summarized statin intolerance definition</th>
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<tbody>
<tr>
<td>International Lipid Expert Panel 12</td>
<td>Inability to tolerate at least two statins, one at low dose, associated with intolerable statin-related adverse effect(s) or biomarker abnormalities that improve with statin decrease/discontinuation.</td>
</tr>
<tr>
<td>NLA (National Lipid Associations) 13</td>
<td>Inability to tolerate at least two statins, one at low dose, due to statin-related objectionable symptoms or abnormal lab determinations that are reversible upon statin discontinuation and reproducible by re-challenge.</td>
</tr>
<tr>
<td>Canadian Working Group 14</td>
<td>Significant symptoms and/or biomarker abnormalities that prevent long-term use of, and adherence to. 2016 indicated use of statins, documented by challenge with at least two statins, including atorvastatin and rosuvastatin.</td>
</tr>
<tr>
<td>ODYSSEY ALTERNATIVE 15</td>
<td>Inability to tolerate ≥2 statins, one at low dose, because of unexplained skeletal muscle-related symptoms (e.g., pain, aches, weakness or cramping) that began or increased during statin treatment and resolved with statin discontinuation.</td>
</tr>
<tr>
<td>GAUSS-2 16</td>
<td>Intolerance of any dose of ≥2 statins or intolerance to increased statin dose because of intolerable myopathy/myalgia, myositis or rhabdomyolysis that improves with statin decrease/discontinuation.</td>
</tr>
<tr>
<td>GAUSS-3 17</td>
<td>Inability to tolerate atorvastatin at 10mg and any other statin at any dose or, alternatively, three or more statins, with one at low dose and two at any dose, followed by muscle-related adverse events on re-challenge and not with placebo.</td>
</tr>
</tbody>
</table>

Adapted from ref. 11.

**Tabella II - Definition of SAMS (from ref. 8).**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Biomarker</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle symptom</td>
<td>normal CK</td>
<td>Often called “myalgia”. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials statin with placebo.</td>
</tr>
<tr>
<td>Muscle symptom</td>
<td>CK &gt;ULN &lt;4x ULN CK &gt;4 &lt;10x UNL</td>
<td>Minor elevation of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin related; this may indicate an increased risk for more severe, underlying muscle problems 19.</td>
</tr>
</tbody>
</table>
The Consensus \(^8\) has provided an accessible resource for the diagnosis, assessment and management of SAMS, as well as an update on current thinking about the aetiology of statin myopathy.

An algorithm (fig. 1) \(^8\) was developed to guide the management of patients with SAMS.

Management of patients with SAMS

When the diagnosis of SAMS is established, different strategies and approaches are proposed. First of all, clinicians should bear in mind that, with appropriate recognition and work-up, most patients with SAMS will be able to tolerate some form of statin therapy, allowing them to attain LDL C goal, and thus derive the important cardiovascular benefits of this therapy. Other options are discussed in those few patients who are unable to tolerate any statin.

Thus, the practical advice is to spend time discussing matters with the patient with SAMS to re-instigate statin treatment with a low dose (e.g., 5 mg atorvastatin), slowly increasing the doses every 4-12 weeks until the maximum-tolerated dose is defined \(^11\). As the next step, the ESC/EAS guidelines recommend combination therapy with ezetimibe \(^1\). Based on the efficacy and safety achieved in the IMPROVE-IT study, combination therapy of statin with ezetimibe is the next option in addition to lifestyle and maximum-tolerated statin dose to reach LDL-targets \(^18\). Alternative combination therapy to statins
and ezetimibe includes bile acid absorption inhibitors, fibrates or PCSK9 inhibitors. Bile acid sequestrants such as cholestyramine, colestipol or colesvelam can be useful in achieving LDL-C goals in combination with statins, reducing LDL-C on average by an additional 10%-20%. However, there are no CV outcome trials of bile acid sequestrants in combination with other drugs.

Fenofibrate lowers LDL-C by 15%-20% in patients with high baseline levels who do not have concomitant hypertriglyceridaemia. Fibrates are easy to take and have shown an acceptable safety record in the ACCORD and FIELD trials. However, additional CVD benefit has not been demonstrated and serum creatinine (and homocysteine) was reversibly increased during treatment. PCSK9 binds to the LDL receptor to target it for degradation; therefore, PCSK9 inhibitors are a promising therapeutic option for reducing LDL-C levels. Initial clinical trial results show promising safety data for anti-PCSK9 antibodies (alirocumab and evolocumab) even in statin intolerant patients. In the GAUSS-2, a phase III, 12-week trial in statin-intolerant patients, the results show that patients on evolocumab (140mg subcutaneously every 2
weeks) experienced a 56% reduction in LDL-C levels compared with 18% in the ezetimibe group. Robust efficacy combined with favorable tolerability makes evolocumab a promising therapy for addressing the largely unmet clinical need in high-risk patients with elevated cholesterol who are statin intolerant. Furthermore, ODYSSEY ALTERNATIVE, a phase III randomized 24-week trial in statin-intolerant patients, an intolerance reaffirmed via placebo run-in and blinded statin re-challenge, demonstrated that alirocumab (75mg subcutaneously every 2 weeks) induced a 45% reduction in LDL-C levels compared with 15% in the ezetimibe group, with fewer skeletal muscle adverse events noted. This was the first study with PCSK9 inhibitors in patients selected with a rigorously documented intolerance to statins, using a placebo run-in and statin control arm.

Although the very promising results achieved by PCSK9 inhibitors in SAMS’ patients, it is important to mention (see also Table II) the difficulties associated with identifying SAMS are reflected in trials with the PCSK9 inhibitors which used varying approaches to select patients with statin intolerance. ODYSSEY Alternative used a placebo run-in to confirm statin intolerance (inability to tolerate ≥2 statins, including one at the lowest approved starting dose). The randomized phase incorporated an atorvastatin re-challenge arm. Here myalgia rates were similar on alirocumab, ezetimibe or atorvastatin, yet in an open label follow-up, <5% of patients developed myalgia on alirocumab.

Instead, GAUSS-317 used an atorvastatin-controlled, double-blind, crossover phase (12 weeks per treatment) to objectively identify patients with muscle symptoms with atorvastatin but not placebo before randomization to evolocumab or ezetimibe. Among patients with statin intolerance related to muscle-related adverse effects, the use of evolocumab compared with ezetimibe resulted in a significantly greater reduction in LDL-C levels after 24 weeks (52.7 vs 16.8%) . Muscle symptoms were reported in 28.8% of ezetimibe-treated patients and 20.7% of evolocumab-treated patients (log-rank P = .17). Active study drug was stopped for muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and 1 of 145 evolocumab-treated patients (0.7%) . Although 43% of patients had muscle pain requiring discontinuation on atorvastatin, 57% of the statin intolerant patients were able to tolerate atorvastatin. Additionally, 27% of patients had muscle pain even when they were receiving placebo.

Already in 2015 the EAS Consensus Panel’s opinion of PCSK9 inhibitors was positive as long as the upcoming long-term outcomes data are favourable. Finally, the FOURIER results is the first demonstration of long-term CVD outcomes benefits with the combination of a statin with a PCSK9 inhibitors thus supporting the pharmacological and clinical values of this class of drugs. Recently, a paper by Lauws U et al. including SAMS expert working group would add a PCSK9 inhibitor to combination therapy (statin, as tolerated, plus ezetimibe) in a high-risk patient with elevated LDL-Cholesterol.

Altogether, the management of SAMS is key in the effective treatment of patients with CardioVascular Disease (CVD), with the final aim to optimize lipid lowering therapy in terms of efficacy, safety and tolerability. Combination therapy with ezetimibe and the addition of PCSK9 inhibitors in high-risk patients with elevated LDL-C is supported by a pharmacological and clinical evidence and is the logical approach to maintain patients on a statin therapy.
REFERENCES

4) Jackevicius CA, Mamdani M, Tu JV et al. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002; 288:462-7
