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Atherosclerosis Supplements 26 (2017) 45–55

ATHEROSCLEROSIS
SUPPLEMENTS

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Practical aspects in the management of statin-associated muscle symptoms (SAMS)

Ulrich Laufs [a,*], Krysztof J. Filipiak [b], Ioanna Gouni-Berthold [c], Alberico L. Catapano [d], and the SAMS expert working group [†]

[a] *Department of Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Saarland University Medical Center, Homburg, Germany*
[b] *First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland*
[c] *Polyclinic for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, Cologne, Germany*
[d] *Department of Pharmacological and Biomolecular Sciences, University of Milan, and IRCCS Multimedica, Milan, Italy*

Abstract

Background and aims: Statin-associated muscle symptoms (SAMS) frequently cause statin non-adherence, switching and discontinuation, contributing to adverse cardiovascular (CV) outcomes. 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. The aim of this article is to provide practical, focused advice for healthcare professionals on the management of patients with SAMS.
Methods: An expert working group combined current evidence, published guidelines and experiences surrounding a number of topics concerning SAMS to provide recommendations on how to best assess and manage this condition and reach the highest tolerated dose of statin for each individual patient.
Results: The group collaborated to provide guidance on definitions in the SAMS field, psychological issues, re-challenging and switching treatments, as well as interpretation of current guidelines and optimal treatment of SAMS in different patient populations. An algorithm was developed to guide the management of patients with SAMS. In addition, the expert working group considered some of the more complex scenarios in a series of frequently asked questions and suggested answers.
Conclusions: The expert working group gave recommendations for healthcare professionals on the management of SAMS but highlighted the importance of tailoring the treatment approach to each individual patient. Evidence supporting the role of nutraceuticals and complementary therapies, such as vitamin D, was lacking, however the majority of the group favoured combination therapy with ezetimibe and the addition of PCSK9 inhibitors in high-risk patients.

Keywords: Statin; Muscle symptoms; Myalgia; Myopathy; Statin intolerance; Lipids; Cholesterol; Cardiovascular disease

Introduction

Statin-associated muscle symptoms (SAMS) are one of the principal reasons for statin non-adherence and/or discontinuation, contributing to adverse cardiovascular (CV) outcomes. Moreover, statin-associated myopathy, with significant elevation of serum creatine kinase (CK), is a rare but serious side effect of statins, affecting 1 per 10,000 people per year on standard statin doses [1]. SAMS cover a broader range of clinical presentations, usually with normal or minimally elevated CK levels, with a prevalence of 7%–29% in registries and observational studies [2].

As the underlying molecular mechanisms of SAMS have not yet been identified, there are currently no specific diagnostic markers or treatments [3]. The aim of this article

* Corresponding author. Department of Internal Medicine III, Cardiology, Angiology and Intensive Care Medicine, Saarland University Medical Center, Homburg, Germany.
E-mail address: Ulrich.Laufs@uniklinikum-saarland.de (U. Laufs).

1567-5688/

is to provide practical, focused advice on the management of SAMS. For that purpose, a group of experts including cardiologists, endocrinologists and internists convened in Barcelona in July 2015. The primary objective was to suggest best practice approaches to common and complex clinical situations. They considered a series of questions on SAMS and made recommendations on how to best assess and manage this condition. This publication contains background information, evidence and guidance that supports the recommendations of the expert working group. The clinical goal is to establish the highest tolerated dose of statin for each individual patient.

How to best define SAMS in clinical practice

Effective treatment of patients with cardiovascular disease (CVD) is limited by reduced tolerance to statins [4]. Understanding and clearly defining SAMS is critical for optimal treatment. Several guidelines and clinical studies have defined statin intolerance (see Table 1) [4–8], but this is not specific for SAMS and a unified widely accepted definition is lacking.

According to the European Atherosclerosis Society (EAS) Consensus Panel, a definitive diagnosis of SAMS is difficult because symptoms are subjective and there is no gold standard diagnostic test [2]. A clinical diagnosis can be made on the basis of a patient's medical history, the clinical presentation and the association of the patient's symptoms (including proximal symmetric pain, tension, stiffness or cramps, associated with muscle stiffness) with statin therapy over time, including after withdrawal and re-challenge [3]. Statin-induced muscle weakness can be detected by myopathic EMG due to myopathic changes, but a normal EMG does not exclude statin-induced myopathy because the latter primarily affects type II muscle fibres [9].

Expert working group opinion on how to best define SAMS in clinical practice

- Assessment and documentation of chronology of symptoms and statin intake is key
- Assess whether the problem relates to physical activity, concomitant medication, diet (grapefruit juice) or musculoskeletal diseases
- In naive patients, if pain and symptoms appearing within the first weeks of treatment are resolved within 2–4 weeks, this will suggest the patient is not statin intolerant
- Consider whether the symptoms carry on after stopping the statins and if the pain is the same on re-challenge
  - If they still have pain after statin discontinuation, then it is not SAMS and should be evaluated further
- Diagnostic testing
  - Genetic testing of SAMS is not helpful
  - There is no blood or imaging test to verify SAMS
  - Electromyography (EMG) could be used to detect primary muscle problems but is not helpful to exclude SAMS
- Most experts recommend the ODYSSEY ALTERNATIVE or GAUSS-2 definition for statin intolerance, although some believe a stricter definition, such as that used in GAUSS-3 is required (see Table 1)

Table 1
Statin intolerance definitions from guidelines and trials

Guideline/RCT	Summarised statin intolerance definition[a]
Unified definition from an International Lipid Expert Panel [4]	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
NLA 2014 [5]	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
Canadian Working Group Consensus 2016 [6]	Significant symptoms and/or biomarker abnormalities that prevent long-term use of, and adherence to, indicated use of statins, documented by challenge with at least two statins, including atorvastatin and rosuvastatin
ODYSSEY ALTERNATIVE [7]	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
GAUSS-2 [8]	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
GAUSS-3 (NCT01984424) [40]	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

[a]For full definitions please see appendix.
NLA, National Lipid Association; RCT, randomised controlled trial.