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Commentary

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Management of Statin-Associated Muscle Symptoms (SAMS) During Lipid-Lowering Therapy (LLT) for Atherosclerotic Cardiovascular Disease (ASCVD)

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Abstract

Statins can decrease lowering level of Low-Density Lipoprotein Cholesterol (LDL-C), and have been effective for prevention of Atherosclerotic Cardiovascular Disease (ASCVD). Lipid-Lowering Therapy (LLT) has been prevalent, but some cases develop statin intolerance. Cases with statin intolerance may show Statin-Associated Muscle Symptoms (SAMS). SAMS includes various clinical manifestations, such as general malaise, mild weakness, muscle pain and cramps with about 5-10% of incidence in clinical practice. European Atherosclerosis Society (EAS) consensus panel included three SAMS types, which are myalgias, myositis and rhabdomyolysis. There is a proposal of algorithm for the management of SAMS with several stages such as genesis, exams, diagnosis, evaluation and management. As non-statin based therapies, ezetimibe and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors can be added and applied.

Key words: Atherosclerotic cardiovascular disease; Low-density lipoprotein cholesterol; American College of Cardiology and American Heart Association; Lipid-lowering therapy; Statin-associated muscle symptoms; Statin intolerance

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Commentary

Across the world, Non-Communicable Diseases (NCDs), lifestyle-related diseases and metabolic syndrome have been in focus for clinical practice [1]. They include diabetes, obesity, dyslipidemia, hypertension and others. These diseases may develop Atherosclerotic Cardiovascular Disease (ASCVD) [2]. Especially, the possibility of ASCVD may be increased by the elevated values of glycosylated hemoglobin (HbA1c) and Low-Density Lipoprotein Cholesterol (LDL-C) [3].

Furthermore, American College of Cardiology and American Heart Association (ACC–AHA) presented the comment for primary prevention of CVD [4]. Both associations proposed the clinical guidelines for management of lipids [5]. Using the guidelines, beneficial management for prevention of ASCVD will be recommended.

Value of LDL-C has been reported to show direct relationship to the risk of ASCVD [6]. Consequently, LDL-C was known as lower is better. When LDL-C becomes lower each 39 mg/dL, cardiovascular event decreases by 22% associated with mortality by 10% [7]. About 30 thousand cases on statin therapy showed the reduction level of LDL-C as 39% [8].

Statins have the function of lowering level of LDL-C, and have been effective in the primary and secondary prevention of ASCVD. Then, statins have been important to continue Lipid-Lowering Therapy (LLT), and given to many patients for years [9]. Among those cases with provided statins, some cases show "statin intolerance". It is defined as "an adverse event by oral administration of statins, which causes unacceptable disorders in daily life, leading to drug discontinuation and dose reduction". It has two situations. One is complete intolerance which is difficult to continue at any given dose of any statin, and another is partial intolerance which is found at certain doses of a particular statin formulation.

Cases with statin intolerance may show Statin-Associated Muscle Symptoms (SAMS) [10]. The most common features of SAMS are in the following: i) developed symptoms within 4-6 weeks after starting statin preparation, ii) involvement of gluteus, flexor thigh, calf, proximal brachial muscle, etc. iii) bilateral symmetry. iv) disappearance by discontinuing the agent for 2-4 weeks. If the same symptoms are reproduced within 4 weeks after re-administration, it is diagnosed that the possibility of SAMS would be high. In such case, changing to other statin products or medications are considered. If the serum Creatine Kinase (CK) value is less than 1000 IU/L, the numerical value itself is not so particularly important but the subjective symptoms should be prioritized for judgment.

SAMS has relevant adverse effect for causing discontinuation of statin meds, leading to subsequently elevated cardiovascular events [9]. The incidence of SAMS seems to be about 5% to 10% in actual clinical practice. SAMS includes various clinical manifestations, such as general malaise, mild weakness, muscle pain and cramps [11]. It rarely causes severe rhabdomyolysis, which needs emergency treatment. SAMS usually shows muscle pains (more than 80%) with and without mild elevation of CK. For patients with SAMS, clinical management includes two steps. The first is discontinuation of statins, and the second is reintroduction of low dose of statin combined with non-statins. Non-statins mean ezetimibe at first, and addition of alirocumab or evolucumab if needed. This protocol may bring meaningful achievement of LDL-C reductions in most cases [12].

Regarding SAMS, clinical spectrum has been heterogeneous, in which it ranges from mild fatigue, muscle pain, cramp to life threatening rhabdomyolysis. European Atherosclerosis Society (EAS) proposed EAS consensus panel that there are three definition of SAMS types [13]. They are i) myalgias: muscle symptoms with normal to mild increased CK, ii) myositis: muscle symptoms plus CK value (upper limit of normal (ULN) x 10<), iii) rhabdomyolysis: muscle symptoms plus CK value (ULN x 40<) plus renal failure [14].

There is a proposal of algorithm for the management of SAMS [12]. It includes several stages as follows: i) genesis: exclusion of exacerbating factors such as drug interaction, exercise, hypothyroidism, etc., ii) exams: laboratory data of CK, TSH, creatinine, vitamin D, etc., iii) diagnosis: judgement for myalgias, myositis or rhabdomyolysis, iv) evaluation: assessment of symptoms severity and confirmation of statin safety, v) management: stop or continue statins, and follow CK and symptoms, vi) restart or not: decision medicine for statins, Ezetimibe or other option. This presents a therapeutic flow chart for SAMS, and some SMAS cases are possibly from vitamin D deficiency [15]. In such case, vitamin D replacement treatment would be reasonable [14].

There have been some recommended methods of LLT. As statin-based therapies, statins at low dose with long half-lives are provided. For example, atorvastatin 5 mg is given on alternate days, or rosuvastatin 5 mg is given 1-3 times per week. Using these methods, LDL-C is expected to be reduced by 25-35% [16]. After reassessment for tolerating this approach in 4-6 weeks, statin and ezetimibe 10mg daily can be added.

In contrast, as non-statin based therapies, we can apply ezetimibe and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors, which are alirocumab and evolocumab [17,18]. Those show clinical efficacy by adding background statin therapy in cases with CVD [18,19].

Concerning ezetimibe, it was firstly recognized non-statin medicine for statin intolerance, which was proposed by European Guidelines for the management of dyslipidemias [20]. It can reduce LDL-C by 15-20% by daily 10mg, and does not develop muscle symptoms. Combined therapy of intermittent low statin and ezetimibe may decrease LDL-C by 40-45% [20].

Regarding PCSK9 inhibitors, they are novel class of hypolipidemics as fully human antibodies that can lower LDL-C value to large extent (approximately less than 60%) [21]. Some studies enrolling patients intolerant for more than 2 statins showed the results that more than 80% cases could tolerate PCSK9 inhibitors with no muscular symptoms [22].

In summary, the management for SAMS patients would be a significant challenge in the clinical practice. It is a strategic approach associated with careful evaluation, reassurance of the case, diagnosis, and gradual restart of low statin amount or other strategy combined with non-statins. This algorithm may bring most patients to tolerate statins, where there are some options of combined with non-statin LLT (ezetimibe±PCSK9 inhibitors) leading to the reduction of LDL-C.

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