

Statin-associated myopathy: a general overview

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ABSTRACT

Among the amazing turn of events in preventing and reducing the risk of cardiovascular diseases since the discovery of statins, thousand of physicians started to prescribe it as a regular life-long treatment, but regarding the expanding number of patients on statin therapy, a wide spectrum of side effects started to appear. Statin-associated myopathy considered as one of the most common side effects and could be subtle for a long time, we performed a review to provide a clinical summary of statin-associated myopathy and to discuss possible mechanisms of risk factors and management of statin-associated myopathy.

Keywords: Statin-associated myopathy, myalgia, myositis, rhabdomyolysis

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Although that cardiovascular diseases considered as the most common cause of death worldwide, but since 2003; death rate has dropped about 38% [1], due to the significant advance in the medical field. However, it has always been the #1 priority is to reduce the incidence and control different risk factors by both life style changes and medical interventions (Drugs, Percutaneous coronary intervention, Surgery).

Guidelines from all over the world (NICE guidelines) consider statins as the drug of choice to control low-density lipoprotein level and reduce the incidence of atherosclerosis which is the most important cause of angina pectoris, myocardial infarction and stroke, but according to the expanding burden of patients with this daily pharmaceutical regime, side effects of this safe groups start to be noticed; as Statin-Associated Myopathy (SAM) considered as one of the most important cause for cessation of the therapy [2].

What is SAM?

Although there is not a universally accepted definition of SAM but it is agreed to refer to any muscular

symptoms occurring during therapy despite of creatine level, and resolve on treatment cessation [3, 4]. SAM considered as one of the most common/severe side effects, the clinical spectrum of SAM include: myalgia, myositis, rhabdomyolysis and asymptomatic elevation of CK [5, 6].

Myalgia

It is the most common condition related to SAM, but as myalgia is frequently reported in hospitals and general clinics and it could for many different reasons, thus statin therapy is not necessarily the cause of myalgia even with the patients on statins therapy [7, 8].

The definition of myalgia is unexplained muscle pain or discomfort, may be described as 'flu-like' general symptoms with normal Creatine Kinase (CK) [8, 9]. The wide spectrum of symptoms include: muscle pain, cramps and maybe associated with weakness [7, 9, 10].

Tenderness after the many articles we reviewed is usually proximal, maybe symmetrical with the involve-



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ment of the large muscle groups such as: the thighs, back muscles and buttocks [11]. Some patients reported legs cramps, difficulty climbing stairs, getting up after sitting. This symptoms aggravated especially during or after exercise, but predominantly without CK elevation [9, 11]. In a review of a database of 508 patients with familial hypercholesterolemia treated with simvastatin (80 mg/day) for two years, myalgia noted in 45 patients with 8.86% [12].

In another observation study (PRIMO), muscle related symptoms was reported by 832 patients out of 7,942 patients with hyperlipidemia receiving statins in an unselected group, with 10.49%, which is relatively close to the percentage of the past study [13]. In general; discomfort or the associated weakness typically occur within the first month (4-6 weeks) after starting the therapy, or symptoms may occur after increasing the dose in a patient who is already on statins, symptoms maybe more frequent in physically active individuals treated with statins [10, 14].

Myositis

Myositis is defined as a muscle inflammation, it is usually accompanied with serum CK elevation; symptoms include pain and weakness and it is typically generalized and proximal (like myalgia) [7, 9, 10]. Skeletal muscle biopsies shows different findings, such as polymyositis and myolysis, however it is not one of the criteria to diagnosis myositis and biopsy is not a routine procedure [6]; so the diagnosis should be considered in any patient with statin therapy in the presence of CK elevation even without any physical or pathological findings [11].

Rhabdomyolysis

It is a rare, life threatening side effect with severe general devastation of the muscles, elevation of serum CK more than 10× of the normal limit, decreased renal function or even failure, myoglobinuria, disseminated intravascular coagulation and maybe death. Symptoms may include: severe muscle pain, muscle weakness through the entire body, dark urine, vomiting, malaise and tachycardia, however patients with rhabdomyolysis may not report any muscular symptoms.

Pathologically biopsies shows myonecrosis and significant inflammation [7, 9, 10, 15]. In one study that included 252,460 patients showed that the average incidence of hospitalization for rhabdomyolysis was

0.44 per 10,000 patients treated with statins (atorvastatin, pravastatin, simvastatin), however; cerivastatin which was withdrawn in 2001 has a 12 fold increased risk in the incidence of rhabdomyolysis. In USA; reported death due to statins induced rhabdomyolysis was over 0.15 per 1000,000 [14, 16, 17].

However; this not a standard universal classification of SAM, and it may be difficult to set a final diagnosis because of the similarity of symptoms and laboratory findings between this three types, and also between other differential diagnosis that mimic SAM findings, and could be much more common.

What are the mechanism of SAM?

Although there is a lot of theories to explain the mechanism of SAM, the etiology still poorly understood, and seems to be multifactorial which need more studies and some of the proposed mechanisms [5, 9, 10, 18, 19].

Membrane ion channels theory

This proposed theory is that impaired synthesis of cholesterol may lead to a different changes in the muscle cell membrane, which may affect membrane fluidity altering ion channels behavior (like sodium, potassium and chloride) affecting the muscle membrane excitability. In an animal study results showed a dose-dependent reduction of membrane chloride conductance in rats treated with simvastatin, while the resting membrane was not affected.

Apoptosis theory

Another proposed theory is statin-induced apoptosis; statin interfere with the synthesis of cholesterol, thus may lead to a pre-cholesterol products depletion such as isoprenoid-lipid. Isoprenoid-lipid depletion involves with myofiber apoptosis. In 'in vivo' studies, statin manage to induce apoptosis in myo cells, but it still not established this particular mechanism 'in vitro'.

Ubiquinone theory

As isoprenoid; ubiquinone (CoQ10) considered as one of the products of cholesterol synthesis pathway, and the depletion of ubiquinone could lead to impaired enzymes activity in mitochondria. However; although low serum concentration of ubiquinone have been noted in patients with statin therapy but the concen-

tration of ubiquinone in muscles have not always showed that. In general myocellular concentration of ubiquinone in patients with statins therapy have showed unchanged, increased and decreased levels. In one small randomized blind trial, 41 patient on statin therapy who had muscle pain, divided into two groups first group (21 patients) received ubiquinone, the other group (20 patients) received vitamin E; after one month of therapy results showed that (18 of 21 patients) who received ubiquinone report improvement in muscle symptoms, compared to (3 of 20 patients) who received vitamin E [20]. However; more studies still needed to confirm the important role of ubiquinone.

Other proposed mechanisms

Autoimmune mechanism, calcium homeostasis impairment and genetics interference.

What are the risk factors of SAM?

Determining and detecting risk factors of SAM before starting statin therapy may help physicians to make more effective and efficient decisions considering statin therapy [2, 4, 6, 9-11]. Risk factors categorized into two types: Patients-related risk factors and therapy-related risk factors.

Patients-related risk factors

This group could be categorized into subtypes:

Demographic: The risk of SAM is higher in:

- >Elderly patients
- >Female sex
- >People with heavy exercise
- >Low body mass index
- >Alcoholism
- >Heavy consumption of grape fruit

Genetics: This is considered as a rare risk factor, it includes such as:

- >Inherited muscle diseases (McArdle, Pompe)
- >Variations in the enzymes system that is responsible of the metabolism of statins (CYP enzymes system)

Co morbidities: Many diseases interfere with statin myotoxicity such as:

- >Renal failure
- >Hepatic failure
- >Hypothyroidism
- >Diabetes mellitus
- >Infections

>Recent major surgery

Therapy-related risk factors

This type divided into subtypes too:

Statin dose: Although the mechanism is unknown; the incidence of SAM increase gradually among the dose and the concentration of statins. Drugs that interfere with CYP2C9 (responsible for the metabolism of rosuvastatin, fluvastatin) such as ranitidine, fluconazole, amiodaron [9, 19].

Combination therapy: Some drugs may increase the incidence of SAM if it was administrated with statins such as fibrates, cyclosporine. Using statins therapy at the same time with gemfibrozile (fibrate) may increase the incidence of rhabdomyolysis approximately 10× higher [9].

Pharmacokinetics: In general; hydrophilic statins are less likely to enter different cells such myocytes, and thus may have less risk of myopathy. However, it is known that hydrophilic statins are as likely as lipophilic statins to cause myotoxicity.

Drug interactions: Interactions with the metabolism of statins (CYP enzymes system): Drugs that interfere with CYP3A4 (responsible for the metabolism of lovastatin, atorvastatin, simvastatin) such as protease inhibitors, macrolide, and diltiazem [9, 19].

What should physicians do to manage SAM?

When patients on statins complain muscle symptoms, detailed history should be taken and physical examination should be done; this procedure covers two goals: first to exclude other more common differential diagnosis, second is to determine the risk factors of SAM [3, 21, 22]. Blood tests, CK and thyroid function (TFT) should be done (hypothyroidism may presents with only hypercholesteremia, raised CK and myalgia), renal function and urine analysis. The first line management is to stop statins, monitor CK and observe symptoms. If muscular symptoms are tolerable and CK is raised less than 10× statin therapy may be continued among with a constant observation. But if there is any signs for rhabdomyolysis or CK level is more than 10× statin therapy should be stopped.

Should physicians monitor CK on a regular basis after statin therapy started?

In general, routine monitoring of CK level is not recommended, but it is useful to obtain a baseline CK

level for comparing purposes prior the starting of statin therapy [3, 11, 22]. For patients receiving statin therapy with an interacting medications it may be necessary to monitor CK level, due to the increased risk of SAM. However; serum CK level does not necessarily exclude muscle damage.

CONCLUSION

Although statins considered as a safe group of drugs, and its benefits of reducing cardiovascular diseases morbidity and mortality, it is still associated with muscular side effects ranging from discomfort to the life-threatening rhabdomyolysis; thus it is important to consider the risk factors of SAM, and assess the advantages and disadvantages for each patient individually before initiating the therapy. Management options for statin-intolerant patients include statin switching, especially to low-dose, non-daily doses of long-acting statins, such as rosuvastatin and atorvastatin. In conclusion, statin-induced myopathy is a significant clinical problem that contributes considerably to statin therapy discontinuation. However, there exist multiple and effective management options for statin intolerant patients [9].

Conflict of interest

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