ISSN: 2456-8090 (online)
DOI: https://doi.org/10.26440/IHRJ/0505.08442

REVIEW

QR CODE

Muscular Adverse Events Associated with Statins

REENA ROYAL[1], NUWAN JAYAWARNDENE*[2]

ABSTRACT

Statins are an important group of lipid lowering medications that have helped to control cardiovascular mortality globally. Muscular side effects, mostly myalgia, is a known adverse event of statins. Intense physical activity, kidney or liver failure, hypothyroidism, inherited or metabolic myopathies, and some medications, are risk factors for statin-induced myalgia. Muscular adverse events are more often observed with higher doses or with the use of lipophilic statins. Much is not known about the precise mechanisms responsible for the statin related muscular adverse effects, a few hypothesis have been suggested. It is important to measure plasma creatine phosphokinase in subjects who encounter myalgia while being treated with statins. In this review we present some general safety information on muscular adverse events caused due to statins.

KEYWORDS: Statins, Myalgia, Side Effects

INTRODUCTION

Statins help to maintain the cholesterol level and decrease cardiovascular complications.[1] They are therefore a widely prescribed therapeutic class. However, several studies indicate that approximately 50% of patients discontinue statin therapy within the first year of prescription.[2,3] There are many reasons for poor adherence to treatment, but the over-occurrence of muscular effects is an important cause. Thus, myalgia on statins is a veritable clinical challenge. In this article, we propose to analyze the different forms of muscle complications under statins, their frequency, the difficulty of their diagnosis, the factors favoring their occurrence, the influence of the dose and the molecule prescribed, the mechanisms involved in statin muscle toxicity, and their management, in clinical practice. Myopathy is used broadly to describe any statin-related muscle side effect. Myalgia describes any muscle pain, without creatine phosphokinase (CPK) elevation.

The term “Myositis" is used for muscle manifestations with increased CPK. Rhabdomyolysis defines a serious complication including muscle pain, significant elevation of CPK (>10 times the upper limit of normal), increased creatinine, and usually dark urine with myoglobinuria. Besides the classic form of statin-induced rhabdomyolysis, a very rare form of statin-induced autoimmune rhabdomyolysis has been described.[4] This rare form, characterized by the presence of anti-HMG-CoA autoantibodies, requires treatment with glucocorticoids, immunosuppressants, and immunoglobulins.[4] The muscle effects of statins represent a continuum from normal CPK muscle soreness to rare cases of rhabdomyolysis. They usually appear a few weeks after initiation of therapy, but can sometimes be seen several years after initiation of statin therapy.

The frequency of muscle complications on statins is difficult to define precisely. In controlled clinical studies, the frequency of muscle side effects is estimated to be between 1.5% and 5.0%.[5] Often, the frequency of muscular side effects does not appear significantly higher in patients on statins than in those on placebo. The rather low frequency of muscle side effects in "controlled" intervention studies may be explained by several reasons: the non-inclusion of mild to moderate muscle pain in the studies, the exclusion of any subject with a history of myopathy on statins or who had muscle pain during the run-in phase, and the biased psychological profile of patients agreeing to participate in clinical studies.[6] Thus, observational studies and daily clinical data show a higher frequency of muscle side effects on statins. In 4% of the patients in the study, there was disabling pain for daily physical activity, and in 0.4%, severe pain requiring cessation of any activity including professional.[7] The US Understanding Statin Use in America and Gaps in Education study found a 25% prevalence of muscle side effects in subjects receiving statin therapy.[8] However,

Submitted on: 03-Jul-2021; **Accepted on:** 19-Aug-2021

the link between reported muscle pain and statin liability is not always clear. Many environmental or cultural factors could also be involved in patients' blaming statin therapy for the occurrence of muscle disorders. For example, in an international survey, the occurrence of unbearable muscle pain on statins was reported in an average of 6% of patients, with significant differences between countries, ranging from 2% for Italy, Spain, Japan and Sweden, to a rate between 10% and 12% for Canada, the UK and the USA.[9] It is highly likely that the frequency of muscle effects of statins is overestimated by patients.[10] These data confirm that not all muscle pain experienced by patients is necessarily related to statins. Thus, while the prevalence of muscle effects on statins is likely to be underestimated by interventional studies, it is clearly overestimated in observational studies and routine clinical practice where any muscle symptomatology presented is not necessarily secondary to statin treatment. However, evidence for a direct effect of statins is provided by a double-blind controlled study objectifying a largely reversible mitochondrial myopathy in patients with normal CPK myalgias on statin.[11]

Diagnosis of statin liability in the face of muscle symptomatology is not obvious, particularly in the absence of CPK elevation. Risk factors for the occurrence of muscle complications on statins include advancing age, female gender, low body mass index, genetic makeup, intense physical activity, kidney or liver failure, hypothyroidism, inherited or metabolic myopathies and excessive alcohol. A few drugs namely fibrates, nicotinic acid, ciclosporin, digoxin, antifungals, macrolides, erythromycin, clarithromycin, protease inhibitors, verapamil, diltiazem and amiodarone are also known risk factors to the occurrence of muscle complications. A genetic polymorphism affecting the OATBP1 transporter, responsible for the uptake of statins by the liver, has been authenticated as a factor increasing the risk of statin myopathy.[12]

Several data strongly suggest that the occurrence of muscle effects is influenced by statin dose. Muscle biopsies from patients with muscle effects secondary to statin use have shown muscle cell necrosis with mitochondrial functional abnormalities.[13] The pathophysiological mechanisms responsible for the muscular effects of statins are not fully elucidated, but several hypotheses have been put forward: Depletion of ubiquinone is a suggested one. The latter is involved in the transport of electrons in the mitochondria and its reduction is likely to impair mitochondrial function. The exact role of ubiquinone, or coenzyme Q10, depletion in the occurrence of statin muscle effects is still debated. Indeed, a study performed after 6 months of treatment with simvastatin 20 mg/d did not demonstrate a decrease in ubiquinone concentration at the muscle level.[14] Another randomized study objectified an efficacy of coenzyme Q10 supplementation in reducing muscle pain on statins.[15] Depletion of isoprenoids is other popular mechanism. It has also been suggested that the reduction of cholesterol content within myocyte membranes may modify the fluidity of the cell membrane, and thus the proper function of ion transporters. This dysfunction of the myocyte membrane could cause cramping and myalgia. This hypothesis remains to be confirmed. Modification of the calcium balance in the muscle cell is another proposed mechanism. Statins inhibit mitochondrial respiratory chain complex with consequent depolarization of the inner membrane promoting calcium efflux from the mitochondria to the cytoplasm.[16]

Excess cytoplasmic calcium is recaptured by the sarcoplasmic reticulum. However, excess calcium within the sarcoplasmic reticulum is released into the cytoplasm via the ryanodine receptor. It has been suggested that statins may also directly activate the ryanodine receptor thereby enhancing excess calcium in the cytoplasm.[16] Calcium overload in the cytoplasm promotes cramping, myalgia and muscle cell apoptosis. Management of myalgia due statins starts with assessment of the intensity and tolerance of the pain, and its nature, whether permanent or transient, as well as possible triggering circumstances, such as unusual physical activity or sports. Concomitant medications that add as a risk factor to myalgia should be considered. If the CPK exceeds 10 times the upper limit of normal, it is imperative to stop the statin and perform urgently a plasma creatinine assay and a myoglobinuria search. Close clinical and biological monitoring should be implemented. In case of frank rhabdomyolysis, vascular filling should be started, without delay. If the CPK level is normal or increased, but less than 10 times the upper limit of normal, the dose of statins should be reduced, or treatment should be withheld altogether. If CPK values exceed 5 times the upper limit of normal or significant muscle pain, transient discontinuation of treatment is strongly advised. If CPK levels are increased, CPK checks should be performed every 1-2 weeks. If muscle pain persists after stopping statin therapy, it is necessary to look for another cause of muscle damage and to perform an

electromyogram. Alternatively, alternating treatments may be suggested like long half-life statins. Before declaring a patient completely statin intolerant, it seems important to try several alternatives with statins and not to abandon statin therapy too quickly. In case of frank intolerance to statins after several attempts, another treatment strategies should be tried.

REFERENCES

1. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999; 282:2340–6.
2. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002;288:455–61.
3. Mann DM, Woodward M, Muntner P, et al. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44: 1410–21.
4. Mammen AL. Statin-associated autoimmune myopathy. N Engl J Med. 2016; 374:664–9.
5. Ward NC, Watts GF, Eckel RH. Statin toxicity. Circ Res. 2019;124:328–50.
6. Vonbank A, Drexel H, Agewall S, et al. Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review. Eur Heart J Cardiovasc Pharmacother. 2018;4:230–6.
7. Bruckert E, Hayem G, Dejager S et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.
8. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6:208–15. https://doi.org/10.1016/j.jacl.2012.03.003
9. Hovingh GK, Gandra SR, McKendrick J, et al. Identification and management of patients with statin-associated symptoms in clinical practice: a clinician survey. Atherosclerosis 2016; 245:111–7. https://doi.org/10.1016/j.atherosclerosis.2015.12.015
10. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, et al; GAUSS-3 investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. JAMA 2016; 315:1580–90.
11. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, et al; Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med. 2002;137: 581–5.
12. SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L et al. SLCO1B1 variants and statin-induced myopathy--a genome wide study. N Engl J Med. 2008;359(8):789-99.
13. Saxon DR, Eckel RH. Statin intolerance: a literature review and management strategies. Prog Cardiovasc Dis 2016; 59:153–64. https://doi.org/10.1016/j.pcad.2016.07.009
14. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. Am J Cardiol. 1996; 77:851–4.
15. Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme Q10 on myopathic symp-toms in patients treated with statins. Am J Cardiol. 2007; 99:1409–12.
16. Sirvent P, Mercier J, Lacampagne A. New insights into mechanisms of statin-associated myotoxicity. Curr Opin Pharmacol. 2008;8:333–8. https://doi.org/10.1016/j.coph.2007.12.010

Source of support: Nil, **Conflict of interest:** None declared

Cite this article as:
Royal R, Jayawardene N. Muscular Adverse Events Associated with Statins. Int Healthc Res J. 2021;5(5):RV5-RV7. https://doi.org/10.26440/IHRJ/0505.08442

AUTHOR AFFILIATIONS: (*Corresponding Author)
1. MD (Internal Medicine), Practicing Medical Specialist, Lumbini, Nepal.
2. B.Sc. Nursing, Mankulam, Sri Lanka.

Contact Corresponding Author at: editor[dot]ihrj[at]gmail[dot]com