ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ "Ο ΕΥΑΓΓΕΛΙΣΜΟΣ"
ΚΑΡΔΙΟΛΟΓΙΚΟ ΤΜΗΜΑ

EVAGELISMOS GENERAL HOSPITAL OF ATHENS
DEPARTMENT OF CARDIOLOGY

July 2014 • Volume 9 • No 3 (35)

ISSN: 1792-7919 e-ISSN: 1792-7927

RHYTHMOS

Editor-in-Chief: Antonis S. Manolis, MD

Editorial Staff: Spyridon Koulouris, MD, Kostas Letsas, MD, Sokratis Pastromas, MD, Ektor Anninos, MD, Effie Rouska, MD

Διευθυντής Σύνταξης: Αντώνης Σ. Μανώλης

Μέλη: Σπυρίδων Κουλούρης, Κώστας Λέτσας, Σωκράτης Παστρωμάς, Έκτωρ Άννινος, Έφη Ρούσκα

URL: www.rhythmos.gr / http://rhythmos.info.tm / http://www.evangelismos.dom.gr

EDITORIAL

Statin-Induced Musculoskeletal Problems: Disconcerting Reports and Data

Antonis S. Manolis, MD

Athens University School of Medicine, Athens, Greece; e-mail: asm@otenet.gr

Statins are molecules of fungal origin, which inhibit the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme, a key step in the sterol biosysnthesis, rendering them powerful cholesterol lowering medications contributing to significant prevention of cardiovascular disease.[1] Statins are characterized by differences in bioavailability, lipo/hydrophilicity, cytochrome P-450 mediated metabolism and cellular transport mechanisms, differences that are reflected in their relative capacity in LDL-cholesterol lowering and possibly in parenchymal or muscular toxicities.[2] Statin intolerance comprises, among others, musculoskeletal problems, such as statin-induced muscle and tendon disorders which are the most common cause of statin discontinuation.[3-10]

Musculoskeletal Problems

Statin therapy has long been associated with musculoskeletal (MS) problems in approximately 10% - 25% of patients treated in real-world clinical practice, but such problems have rarely been reported in controlled clinical trials,[3,4] and their incidence has thus far been underestimated.[5] Studies have concentrated on creatine kinase (CK) elevations to identify myopathy. However, many patients can have normal serum CK levels despite myalgia and persistent weakness and muscle biopsy - proven myopathy. Discontinuation of statin and rechalllenge may be required to prove that it is statin-related. Several risk factors may predispose patients to statin-related MS problems, including advanced age, family history of myopathy, statin dose, and interacting medications (e.g., azole antifungals, cimetidine, fibrates, macrolide antibiotics, protease inhibitors and cyclosporine) (Table 1).[5,6,8]

Musculoskeletal conditions, arthropathies, injuries, and pain appear to be more common among statin users than among similar nonusers. In a recent retrospective cohort study (N= 46,249; 13 626 statin users and 32 623 nonusers) with propensity score matching (n=6967 statin users; n= 6967 nonusers),[7] the authors investigated whether statin use is associated with musculoskeletal conditions, including arthropathy and injury, in a military health care system. Statin-associated musculoskeletal adverse effects include a wide array of clinical presentations, including myalgias, muscle weakness, muscle cramps, rhabdomyolysis, autoimmune muscle disease, and tendinous diseases. Among matched pairs, statin users had a higher odds ratio (OR) for all musculoskeletal diseases (OR, 1.19), injury-related diseases (dislocation, sprain, strain) (1.13), and drug-associated musculoskeletal pain

(1.09); the OR for arthropathies and related diseases was 1.07 (P = 0.07). Secondary and sensitivity analyses revealed higher adjusted ORs for statin users in all outcome groups. The authors concluded that musculoskeletal conditions, arthropathies, injuries, and pain are more common among statin users than among similar nonusers.

A recent large cohort study reporting on discontinuation of statins in routine care settings indicated that statins were discontinued at least temporarily for 57,292 out of 107,835 patients.[9] Statin-related events were documented for 18,778 (17.4%) patients, - a substantially higher rate than the 5-10% rate usually described in randomized placebo-controlled clinical trials. Similar to both clinical trials and observational studies, musculo-skeletal symptoms predominated - accounting for 40% of statin-related events. However, overt rhabdomyolysis was found in only 0.006% of the study patients, also consistent with previous reports that statin-induced severe myopathy is a rare event. In this study, the majority (>90%) of patients who were rechallenged with a statin after a statin-related event, were finally able to tolerate one. The authors concluded that statin-related events are commonly reported and often lead to the discontinuation of statins; nearly 1 in 5 patients in this cohort stopped all statins for at least 12 months. However, most patients who are rechallenged can tolerate statins long-term. This suggests that many of the statin-related events may have other etiologies, are tolerable or may be specific to individual statins rather than the entire drug class.

Table 1. Risk Factors for Developing Statin-Related Musculoskeletal Problems

Age > 75-80 years old	**Drugs**
Female gender	Fibrates
Low BMI, frail	Cyclosporine
History (or FH) of muscle symptoms / disease / ↑CK	Protease inhibitors
History (or FH) of statin intolerance	Antibiotics: Macrolides / Daptomycin/ Antifungals (Azole) / Rifampin/ Fusidic acid
Renal / Liver disease	Ranolazine
Diabetes	Amiodarone/Dronedarone
Vitamin D deficiency	Verapamil/Diltiazem
Hypothyroidism	Cocaine
High-dose statin	Danazol
Type of statin	Warfarin
Physical exercise	Cimetidine
Major surgery	Nefazodone
Genetic polymorphisms	Colchicine
Grapefruit juice	Nicotinic acid
Alcohol	Dasatinib

BMI = body mass index; CK = creatine kinase; FH = family history

Myopathies

The above and other recent papers on statin-induced myopathy have lately spawned an intense discussion and controversy regarding the results of randomized controlled trials reporting a much lower incidence of such adverse effects.[7,9,11-14] A recent review and meta-analysis of observational studies has confirmed the increased incidence of statin-related myopathy with an odds ratio of 2.63,[15] further fueling the heated discussion emanating from the recent guidelines recommending an expansion of the population base to receive statins. The authors of this review indicate that their analysis giving higher estimates than randomized controlled trials for myopathy may reflect differences in the diagnostic criteria used and the populations studied. They emphasize that myopathy is more likely to occur with higher doses of statins and randomized controlled trials have excluded situations that raise statin blood levels, including advanced age, frailty, deterioration of renal function and the presence of interacting drugs.

The spectrum of statin-related myopathies ranges from common, albeit clinically benign, myalgia without CK elevation to typical myositis with CK elevation to rare but life-threatening rhabdomyolysis. It is estimated by observational studies that 10 - 15% of statin users develop statin-related muscle side effects. Fortunately, the more severe form of rhabdomyolysis remains rare.[3-9]

The mechanisms of statin-related myopathies have not been clearly elucidated. However, strong evidence has emerged from observational and clinical studies that skeletal muscle toxicity is a dose-dependent feature associated with all statins, with some (lipophilic) statins being more toxic than others (hydrophilic statins), primarily related to the reduced availability of metabolites produced by the mevalonate pathway rather than intracellular cholesterol lowering per se which include alteration in isoprenoids synthesis.[16] In general, there is a complex interplay between drug–environment and drug–drug interaction in the context of different genetic settings contributing to statin-induced skeletal muscle toxicity. Of note, an important metabolite derived from cholesterol is vitamin D, produced when 7-dehydrocholesterol is converted by ultraviolet B light to active vitamin D3 in the skin. Importantly, vitamin D deficiency can cause muscle weakness, generalized muscle pain, and levels of vitamin D <30 nmol/L are associated with decreased muscle strength. Indeed, a cross-sectional study showed that low levels of vitamin D were associated with increased statin-induced skeletal muscle complaints [17] suggesting a reversible interaction between vitamin D deficiency and statins on skeletal muscle. However, the role of vitamin D

on induction or protection from muscle toxicity during statin therapy remains unclear.

Options for managing statin myopathies include lower dose of statin, statin switching, particularly to fluvastatin or low-dose rosuvastatin; nondaily dosing regimens;[18,19] nonstatin alternatives, such as ezetimibe and bile acid-binding resins (colesevelam); and coenzyme Q10 supplementation. However, the evidence supporting such strategies remains scanty. Re-initiation of statins in a patient who has exhibited statin-related MS problems should be individualized and caution should be exercised.[20,21] If the diagnosis of statin-induced myopathy was correct and there were no modifiable risk factors, the likelihood is high that the problem will recur upon rechallenge with same statin at the same dose. A modified approach by switching to another statin and using a low dose may reduce the risk of recurrence.

Statin-related myopathies will probably become more prevalent in the future with greater numbers of persons being placed on statin therapy, as recommended by the recent ACC/AHA guidelines,[1,8] despite the controversy they have invoked, and thus there is need for further research to better identify patients at risk for statin myopathy and to evaluate management strategies for statin-related myopathy.

Tendinopathies

In addition to muscle toxicity, statins have also been implicated in drug-induced tendon toxicity, which is rare but often underestimated. [7,22] Statins are among the four main drug classes which have been incriminated in tendinopathies, [23] with quinolones and long-term glucocorticoids being the most widely known, but statins and aromatase inhibitors can also induce tendon damage. The pathophysiological mechanisms underlying drug-induced tendinopathies remain unknown. Identified risk factors may include age >60 years, pre-existing tendinopathy, and drug combinations potentiating these toxic effects. Mean time to symptom onset varies among the drug classes and reaches several months for statins. The most frequent sites of involvement are the lower limb tendons, most commonly the Achilles tendon. The most dramatic clinical manifestation of tendininous disorders is tendon rupture.[10,24,25] Tendon rupture usually occurs in injured tendons. Physiological repair of an injured tendon requires degradation and remodeling of the extracellular matrix through matrix metalloproteinases (MMPs). The authors of a statin-related spontaneous biceps tendon rupture have put forth the hypothesis that statins may increase the risk of tendon rupture by inhibiting MMP activity.[24]

French investigators have analyzed 96 reports of tendon disorders attributed to statins.[10] Patients had tendinitis (66%) and tendon rupture (34%). The Achilles tendon was most often affected. This adverse effect mainly occurred during the first year of treatment and appeared to be more frequent in patients with diabetes, hyperuricemia or a history of tendon disorders, and in persons engaging in strenuous sports. Reinitiation of statin in a few cases results in recurrence of tendinopathy in all cases. In practice, tendinopathy appears to be a rare adverse effect of statins, but patients should be closely monitored during the first year of treatment, especially when they have associated risk factors.

Autoimmune Necrotic Myositis

Persistent weakness after statin withdrawal has also been reported, attributed to severe form of *autoimmune necrotic myositis* triggered by statins; successful treatment has been applied with use of intravenous immunoglobulins, combined with steroids and metothrexate.[26] Detection of serum antibodies to the target enzyme of statins (3-hydroksy-3-methylglutaryl-coenzyme A reductase) has been reported in cases of inflammatory and necrotizing myopathies.[27,28] Even *myasthenia gravis* has been associated with intake of statins. [29]

Statin Muscle Safety Task Force

Recently, a Statin Muscle Safety Task Force, the National Lipid Association's Muscle Safety Expert Panel, was convened and charged with the duty of examining the definitions for statin-related MS problems, development of a clinical index to assess myalgia, and the use of diagnostic neuromuscular studies to investigate muscle adverse events.[30] The Panel developed an algorithm for the evaluation and treatment of patients who may be intolerant to statins as the result of adverse muscle events. The Panel has attempted to answer this year's questions. The answer was affirmative to the first question of whether statin-associated myalgia could be reliably differentiated from myalgia associated with a placebo, based on the results of the STOMP trial.[31] For this purpose, the suggested standard definition of statin-related myalgia includes:

- new-onset or increased symptoms of myalgia (muscle aches, stiffness, cramping, soreness, and tenderness) that are unassociated with recent exercise;
- symptoms that persist for at least 2 weeks;
- symptoms that resolve within 2 weeks of stopping the study drug; and
- symptoms that recur within 4 weeks of restarting the medication.

The Panel admitted that there have been no validated scales to diagnose statin-associated myalgia. Nevertheless,

they propose a quantitative myalgia score that is largely based on the findings from the STOMP trial.[31] This statin myalgia clinical index score rates the symptoms as probable, possible, or unlikely related to statin. Statin-associated muscle pain usually affects the lower limbs, as reported in the PRIMO study,[3] and are likely to occur within the first month of therapy.

The Panel indicated that statins are less tolerated in physically active individuals, as the statin-associated muscle complaints are proportional to the acute and chronic physical activity.[30] The data suggest that statin therapy may produce a greater incidence of muscle-related side effects in chronically physically active individuals and may also exacerbate skeletal muscle damage and CK release during acute exercise. The Panel also provided diagnostic criteria for statin-induced myopathy, which include proximal weakness detected on physical examination and standardized muscle testing and finally confirmed by electromyography plus/minus muscle biopsy. For the timing of muscle biopsy, the Panel recommended to start with an electromyogram (EMG), and to proceed to biopsy in those individuals with fibrillations and/or positive sharp waves in the affected muscles to assist in correctly diagnosing the type of muscle disorder that is responsible for the CK elevation, after a thorough neurological examination has excluded certain neuropathies and radiculopathies.

The Panel also agreed that according with retrospective data derived from registries, most (~90%) patients who are intolerant to one statin because of myalgia can generally tolerate a different statin.[30] Although some propose a statin that is independent of cytochrome P450 3A4 metabolism such as pravastatin, rosuvastatin, fluvastatin, or pitavastatin, there have been no randomized studies confirming this recommendation. Some have suggested that lipophilic statins (simvastatin/lovastatin) are more likely to produce muscular effects as opposed to the more hydrophilic statins (pravastatin, rosuvastatin, and fluvastatin), but again this needs to be put to test by appropriately designed studies. Others have related the muscle toxicity to specific drug potency, with relative adverse event risks being higher with higher potency statins.[32]

For statin-intolerant patients, the Panel recommends alternate-day or non-daily dosing with statins of long half-life (rosuvastatin and atorvastatin),[19] although these dosing regimens have not been studied in terms of their effectiveness in reducing cardiovascular events. [18,30] Finally, when all else has failed, nonstatin LDL-C-lowering therapies (ezetimibe, colesevelam) may be employed or added to low-dose statin therapy. Supplemental use of vitamin D or coenzyme Q10 has also been suggested but remains to be proven effective.

REFERENCES

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the ACC/AHA Task Force on Practice Guidelines. ***J Am Coll Cardiol*** 2014;63(25 Pt B):2889-934.
2. Sirtori CR. The pharmacology of statins. *Pharmacol Res* 2014 Mar 20. [Epub ahead of print]
3. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. ***Cardiovasc Drugs Ther*** 2005;19:403-414.
4. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. ***Am Heart J*** 2014;168:6-15.
5. Rallidis LS, Fountoulaki K, Anastasiou-Nana M. Managing the underestimated risk of statin-associated myopathy. ***Int J Cardiol*** 2012; 159: 169–176.
6. Sathasivam S. Statin induced myotoxicity. ***Eur J Intern Med*** 2012; 23: 317–324.
7. Mansi I, Frei CR, PharmD, Pugh M, Makris U, Mortensen EM. Statins and musculoskeletal conditions, arthropathies, and injuries. ***JAMA Intern Med*** 2013;173:1-10.
8. Ahmad Z. Statin intolerance. ***Am J Cardiol*** 2014;113:1765-1771.
9. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. ***Ann Intern Med*** 2013;158:526-34.
10. Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C; Network of the French Pharmacovigilance Centers. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990-2005 and review of the literature. ***Arthritis Rheum*** 2008;59:367-372.
11. Godlee F. Adverse effects of statins. ***BMJ*** 2014;348:g3306.
12. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? ***BMJ*** 2013;347:f6123.
13. Malhotra A. Saturated fat is not the major issue: let's bust the myth of its role in heart disease. ***BMJ*** 2013;347:f6340.
14. Fahey T, Smith S. Retraction of statins article is not in the public interest: better characterisation of benefits and risks is crucial. ***BMJ*** 2014;348:g4028.
15. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. ***BMC Med*** 2014;12:51.
16. Norata GD, Tibolla G, Catapano AL. Statins and skeletal muscles toxicity: From clinical trials to everyday practice. ***Pharmacol Res*** 2014 May 13. [Epub ahead of print]
17. Ahmed W, Khan N, Glueck CJ, Pandey S, Wang P, Goldenberg N, et al. Low serum25(OH) vitamin D levels (<32 ng/ml) are associated with reversible myositis-myalgia in statin-treated patients. ***Translat Res*** 2009;153:11–16.
18. Marcus FI, Baumgarten AJ, Fritz WL, Nolan PE Jr. Alternate-day dosing with statins. ***Am J Med*** 2013;126:99-104.

19. Elis A, Lishner M. Non-every day statin administration--a literature review. ***Eur J Intern Med*** 2012;23:474-478.
20. Wilkinson MJ, Laffin LJ, Davidson MH. Overcoming toxicity and side-effects of lipid-lowering therapies. ***Best Pract Res Clin Endocrinol Metab*** 2014;28:439-452.
21. Brito JP, Montori VM. Reinitiation of statins after statin-associated musculoskeletal symptoms: a patient-centered approach. ***Circ Cardiovasc Qual Outcomes*** 2013;6:243-247.
22. Chazerain P, Hayem G, Hamza S, Best C, Ziza JM. Four cases of tendinopathy in patients on statin therapy. ***Joint Bone Spine*** 2001;68:430-433.
23. Kirchgesner T, Larbi A, Omoumi P, et al. Drug-induced tendinopathy: From physiology to clinical applications. ***Joint Bone Spine*** 2014 Jun 21. [Epub ahead of print]
24. Pullatt RC, Gadarla MR, Karas RH, Alsheikh-Ali AA, Thompson PD. Tendon rupture associated with simvastatin/ezetimibe therapy. ***Am J Cardiol*** 2007;100:152-153.
25. Carmont MR, Highland AM, Blundell CM, Davies MB. Simultaneous bilateral Achilles tendon ruptures associated with statin medication despite regular rock climbing exercise. ***Phys Ther Sport*** 2009;10:150-152.
26. Mygland Å, Ljøstad U, Krossnes BK. Persisting weakness after withdrawal of a statin. ***BMJ Case Rep*** 2014 Apr 8;2014. pii: bcr2013203094. doi: 10.1136/bcr-2013-203094.
27. Padala S, Thompson PD. Statins as a possible cause of inflammatory and necrotizing myopathies. ***Atherosclerosis*** 2012;222:15-21.
28. Hamann PD, Cooper RG, McHugh NJ, Chinoy H. Statin-induced necrotizing myositis - a discrete autoimmune entity within the "statin-induced myopathy spectrum". ***Autoimmun Rev*** 2013;12:1177-1181.
29. Gale J, Danesh-Meyer HV. Statins can induce myasthenia gravis. ***J Clin Neurosci*** 2014;21:195-197.
30. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. ***J Clin Lipidol*** 2014; 8(3 Suppl):S58–S71.
31. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. ***Circulation*** 2013;127:96–103.
32. Hoffman KB, Kraus C, Dimbil M, Golomb BA. A survey of the FDA's AERS database regarding muscle and tendon adverse events linked to the statin drug class. ***PLoS One*** 2012;7(8): e42866.

REVIEW

Beta-Blockers in Post-MI Patients: Need to Re-consider?

Prokopis Papadimitriou, MD, Antonis S. Manolis, MD
Department of Cardiology, Evagelismos Hospital,
Athens, Greece

Abstract

International clinical practice guidelines recommend early introduction and continued treatment with beta-blockers for all patients without contraindications after STEMI. Although there seemed to be little question that patients with STEMI, regardless of revascularization strategy, derive substantial benefits from both long- and short-term beta-blockade, there has been a paucity of high quality evidence supporting this notion and the majority of data predate modern reperfusion therapy and current medical management strategies with statins and antiplatelet agents. Recently published data question this "one-size-fits-all" approach, showing that the use of beta-blockers increased the risk of heart failure and cardiogenic shock with no mortality benefit.

Key Words: acute myocardial infarction; beta-blockers**;** heart failure; cardiogenic shock

List of Abbreviations

AMI = acute myocardial infarction; EF = ejection fraction; ICD = implantable cardioverter defibrillator; HF = heart failure; LV = left ventric-le(-ular); MACE = major cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RAAS = renin-angiotensin aldosterone system; STEMI = ST-elevation myocardial infarction; VF = ventricular fibrillation

Introduction

Beta adrenergic receptor blockers have long been recommended for the treatment of all stages of ischemic heart disease, with the exception of Prinzmetal's vasospastic variant angina. Beta-Blockade is still regarded as standard therapy for effort angina, mixed effort and rest angina, and unstable angina. International clinical practice guidelines recommend beta-blocker therapy, both short- and long-term, to all acute coronary syndrome patients without contraindications, regardless of the revascularization strategy. However, much of the data to support their use predates reperfusion and contemporary medical therapy, while controversy also exists over the optimum timing of therapy initiation and discontinuation.

Mechanisms of beta-blockers action

Potentially beneficial effects of beta-blockers in patients with acute myocardial infarction (MI) include: [1,2]