|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Volume 4, Issue 1; January: 2020; Page No. 269-271

STATIN INTOLERANCE: CURRENT STATUS AND MANAGEMENT

Dr. Ajay Gupta[1], Dr. Nisha Gupta[2]
[1]Department of Endocrinology and Medicine, Assistant Professor, Index Medical College & Research Center, Indore & MD (Medicine), DM (Endocrinology) AIIMS
[2]MBBS, DOMS Consultant, Apple hospital Indore

Article Info: Received 06 January 2020; Accepted 28 January. 2020
DOI: https://doi.org/10.32553/ijmbs.v4i1.974
Corresponding author: Dr. Ajay Gupta
Conflict of interest: No conflict of interest.

Introduction

Statins (HMG-CoA reductase inhibitors), since their introduction in 1987 are considered the first-line pharmacotherapy for cholesterol reduction. Because of their proven therapeutic ability to prevent cardiovascular disease and to extend life, statins are among one of the most widely prescribed medications. Various randomized clinical trials have consistently shown that statins have a beneficial role in both primary and secondary prevention strategies, with a significant reduction in major vascular events, including death, myocardial infarction, stroke, and coronary revascularization[1].

Statin intolerance is the inability to tolerate a dose of statin required to reduce a person's CV risk sufficiently from their baseline risk and could result from side effects, mainly muscle- and liver-related [2-4]. In addition, some other less common side effects may lead to statin discontinuation (e.g., nephrotoxicity, peripheral neuropathy, memory loss, sleep disturbances and erectile dysfunction, gynecomastia, and/or arthritis) [2]. The intolerance can be either partial (ie, only some statins at some doses) or complete (ie, all statins at any dose).

Clinical aspects and risk factors of statin-associated adverse effects

In clinical practice, statin intolerance limits effective treatment of patients at risk of, or with, CV disease. Fortunately, statins are generally very well tolerated with a very low risk of serious adverse outcomes. According to available data, side effects are class-dependent, dose-dependent, time-dependent, age-, gender- and co-morbidity dependent, and/or dependent on co-treatment with certain drugs or foods. The various risk factors which are associated with increased risk of statin associated side effect is shown in table 1. Adverse effects of statin therapy for which there is solid evidence are shown in Table 2. However, numerous other adverse effects that have been anecdotally attributed to statin treatment have no objective evidence to support any cause-and-effect relationship (Table 2).

Most adverse effects associated with statin therapy are muscle-related. The clinical presentation of statin myopathy varies from myalgia to rhabdomyolysis requiring hospitalization. The most frequently reported symptoms include muscle weakness, myalgia, fatigue, generalized aching, and low back or proximal muscle pain.[.5-7] According to well accepted definitions, myalgia is defined as muscular symptoms without CK elevations; myositis refers to muscle symptoms with CK elevation; and rhabdomyolysis is defined as muscle symptoms with marked CK elevations (>10 times ULN) with an elevated plasma creatinine and the occasional presence of brown urine[7].

The most commonly encountered hepatic biochemical abnormality during statin therapy is the asymptomatic elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which appears to be a class effect of statins [5]. According to statement from 28th February 2012 the Food and Drug Administration (FDA) recommends checking liver function tests at baseline and later as clinically warranted [8].

Statin therapy may increase the risk of new onset diabetes mellitus (NOD) this association is observed for all investigated statins (hydrophilic or lipophilic), thus possibly representing a class effect [9,10] However this risk is very small and is almost completed outweighed by the benefits of statins. Treatment of 255 people with statins for 4 years results in 1 additional case of diabetes mellitus. In those 255 individuals, statin treatment over the same time period would have prevented at least 5 serious cardiovascular events such as heart attack and stroke[11].

Table 1: Risk factors for statin-induced side effects

High dose statin therapy
Vitamin D deficiency
Advanced age (> 70 years)
Female sex
Family history of muscle disorders
History of CK elevation,
Renal impairment

Hepatic impairment
Previous history of muscle toxicity with another lipid-lowering therapy
Untreated hypothyroidism
Disorders' of calcium homeostasis
Alcohol abuse
Asian ethnicity
Low body mass index (BMI)
Genetic polymorphisms (e.g. genes associated with drug and muscle metabolism, CYP450 variants, drug transporter variants)
Surgery with severe metabolic demands
Heavy and/or unaccustomed exercise
Interactions with concomitant medication
Excessive grapefruit juice intake

Table 2: Potential Adverse Effects of Statins

Adverse effects for which there is good supportive evidence
Myopathy (myalgia, myositis, rhabdomyolysis)
Increase in liver function enzymes
New-onset diabetes mellitus
Adverse effects for which there is little or no supportive evidence
Cancer
Intracerebral hemorrhage (bleeding stroke)
Cognitive decline (Alzheimer disease)
Lung disease
Erectile dysfunction, gynecomastia
Fatigue, headaches, or dizziness
Psychiatric illness
Cataracts, diplopia, ptosis and ophthalmoplegia
Tendinitis, arthralgia, arthritis, lupus, polymyalgia rheumatica
Gastrointestinal upset, abdominal cramping
Permanent liver or kidney damage

Discussion

Management of Statin Intolerance

Benefit of statin are large and potentially lifesaving and any risks of side effects are small, not life threatening, and reversible. The reduction in fatal and nonfatal heart attack and stroke by statin treatment cannot be achieved with other currently available lipid lowering medications, nutraceuticals, or dietary modifications. Statin-induced elevation of CK levels > 10 times the upper limit of normal and hepatic transaminases >3 times the upper limit of normal) have been reported as good predictors of serious statin intolerance.[12]

The presence of contributing factors, such as hypothyroidism, vitamin D deficiency, strenuous exercise and consumption of grapefruit juice, should be assessed. Medications that inhibit CYP3A4 (such as azole antifungals, macrolide antibiotic, fibrates, and calcium channel blockers), or CYP2C9 (such as amiodarone) should be ruled out.

Statin-based approaches

Switching statins may be efficacious. Considering the results of the PRIMO study, the use of statins associated with a lower risk of myopathy, such as fluvastatin or pravastatin, may be considered [13], another approach evaluated in several studies involves the use of long-acting

statins, mainly rosuvastatin, in low doses or at a reduced frequency (1–3 times a week).

The current 2013 ACC/AHA guidelines [14] recommend that a patient who develops statin intolerance be given a lower dose of the same statin or an alternative appropriate statin until a statin and a dose that have no adverse effects have been identified.

Nonstatin medications

When no statin is tolerated, non statin therapies should be used. The most commonly used drug is ezetimibe. Another option to reduce cholesterol absorption is the use of bile acid sequestrants

(BAS), which were proven to reduce cardiovascular events in the Lipid Research Clinics Study Coronary Primary Prevention Trial (LRC-CPPT) [15]. Niacin at daily doses from 500 to 2,000 mg lowers LDL cholesterol by ~20%. The use of niacin is limited by its side effects,mainly flushing, which can lead to the drug being discontinued in up to 25% of patients [16].

PCSK9 inhibitors can for patients who are statin intolerant.Pharmacological agents under development like Cholesterol ester transfer protein (CETP) inhibitors may be available in near future for management of dyslipedemia and may be used in statin intolerant patients.

Nonpharmacological approaches

Nonpharmacological therapies should be part of every patient's lifestyle, and they become particularly important when a patient is faced with statin intolerance. A diet low in saturated fats, the use of polyunsaturated and monounsaturated fats, specific diets (such as the Portfolio diet or Mediterranean diet), plant sterols, and viscous fiber are all associated with modest reductions in

LDL cholesterol and can help to keep the dose of statin low.

Conclusion

In statin-intolerant patients at high risk of cardiovascular events, all efforts should be made to reduce LDL cholesterol to as close as possible to target levels, using lifestyle measures and combinations of nonstatin drugs. There is a need for standardization of definitions for statin

intolerance, as well as for clinical trials designed with the statin-intolerant patient in mind, to provide more insight into management and outcomes for the clinician.

References

1. Stone, N.J., *et al.* 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol*. (2013)
2. Ganga HV, Slim HB, Thompson PD.A systematic review of statin-induced muscle problems in clinical trials.Am Heart J 2014;168:6-15
3. Rosenson RS, Baker SK, Jacobson TA,et al. An assessment by the Statin Muscle Safety Task Force: 2014 update.J Clin Lipidol ,014;8(3 Suppl):S58-71
4. Guyton JR, Bays HE, Grundy SM, et al. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol 2014;8(3 Suppl):S72-81
5. Armitage J. The safety of statins in clinical practice. *Lancet*. 2007;370(9601):1781–1790
6. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr Opin Lipidol*. 2007;18(4):401–408.
7. Toth PP, Harper CR, Jacobson TA. Clinical characterization and molecular mechanisms of statin myopathy. *Expert Rev Cardiovasc Ther*. 2008;6(7): 955–969.
8. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs (2-28-2012). http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm
9. Katsiki N, Banach M. Statin use and risk of diabetes mellitus in postmenopausal women. Clin Lipidol 2012; 7: 267-70.
10. Barylski M, Małyszko J, Rysz J, Myśliwiec M, Banach M.Lipids, blood pressure, kidney – what was new in 2011? Arch Med Sci 2011; 7: 1055-66.
11. David H. Fitchett, Robert A. Hegele et al. Statin Intolerance. *Circulation*. 2015;131:e389-e391
12. Mancini GB, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, *et al*. Diagnosis, prevention, and management of statin adverse effects and intolerance: Proceedings of a canadian working group consensus conference. Canad J Cardiol 2011;27:635-62.
13. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patientsdthe PRIMO study. Cardiovasc Drugs Ther2005;19:403–414
14. Keaney, J.F. Jr, Curfman, G.D. & Jarcho, J.A. A pragmatic view of the new cholesterol treatment guidelines. *N. Engl. J. Med*. **370**, 275–278 (2014).
15. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heartdisease. JAMA 1984;251:351–364
16. AIM-HIGH Investigators. Boden WE,Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levelsreceiving intensive statin therapy. N Engl J Med 2011;365:2255–2267