Review Article

Management of statin intolerance

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ABSTRACT

Statins are the revolutionary drugs in the cardiovascular pharmacotherapy. But they also possess several adverse effects like myopathy with elevation of hepatic transaminases (>3 times the upper limit of normal) or creatine kinase (>10 times the upper limit of normal) and some rare side-effects, including peripheral neuropathy, memory loss, sleep disturbances, and erectile dysfunction. Due to these adverse effects, patients abruptly withdrew statins without consulting physicians. This abrupt discontinuation of statins is termed as statin intolerance. Statin-induced myopathy constitutes two third of all side-effects from statins and is the primary reason for statin intolerance. Though statin intolerance has considerably impacted cardiovascular outcomes in the high-risk patients, it has been well effectively managed by prescribing statins either as alternate-day or once weekly dosage regimen, as combination therapy with a non-statin therapy or and by dietary intervention. The present article reviews the causes, clinical implications of statin withdrawal and management of statin intolerance.

Key words: Adverse effects of stains, myopathy, rhabdomyolysis, statins, statin intolerance

Introduction

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have revolutionized cardiovascular pharmacotherapy. Though they have confirmed safety and efficacy profile, statins have reportedly been associated with several adverse effects forcing abrupt discontinuation without consulting their physician.[1] This is termed as statin intolerance. Statins were shown to adversely affect fatty acid oxidation, decrease sarcolemal cholesterol, deplete isoprenoid, disturb calcium homeostasis and lipid metabolism, cause autoimmune phenomena, increase intracellular lipids, and cause mitochondrial dysfunction due to inhibition of ubiquinone or coenzyme Q10 production, leading to emergence of statin-induced adverse effects [Table 1].[2] The major statin-induced adverse effects are muscle-related complications (myalgia, myopathy, rhabdomyolysis), hepatotoxicity, nephrotoxicity (proteinuria), headache, rash, and gastrointestinal discomforts.[3,4] These adverse effects manifest more severely in patients aged over 80 years, with liver and muscle disorders, chronic renal insufficiency with diabetes or hypothyroidism, or co-prescription of agents that compete with statins for metabolism such as fibrates, cyclosporine, warfarin, azole antifungals, macrolides, Human Immunodeficiency Virus (HIV) protease inhibitors, verapamil or amiodarone.[4] Predominantly, myalgia is considered as the leading cause of statin intolerance.[5,6] Both myopathy and rhabdomyolysis constitute two thirds of statin adverse effects that warrant serious attention. Fatal incidence of rhabdomyolysis was considered as the major reason of cerivastatin withdrawal in 2001.[7] As per Food and Drug Administration, myopathy is defined as elevation of creatinine kinase (CK) up to 10-fold, myalgia as any pain in a muscle or group of muscles, and rhabdomyolysis as CK elevation >50-fold with severe skeletal muscle injury and lysis and myoglobinuria. Other rare adverse effects of statins-peripheral neuropathy, memory loss, erectile dysfunction, and sleep disturbances may also lead to statin intolerance [Table 3].

In clinical practice, statin intolerance poses a great hindrance to effective treatment in patients afflicted with cardiovascular disease, leading to statin discontinuation in 28.9% of patients within the first year of initiation of statin therapy.[8]

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Table 1: Mechanism of major statin-induced adverse effects

Adverse effects	Mechanisms	References
Myopathy/rhabdomyolysis (CK>10x ULN)	Isoprenoid depletion (F-PP and GG-PP): Dysprenylation of small GTPases (Rac, Rho etc.,) and lamins→↑cytosolic calcium, caspase 3 activation and cell death Blocks farnesyl pyrophosphate→Inhibition of ubiquinone or coenzyme Q10 synthesis in mitochondria→Impaired energy production, ↓Sarcolemal cholesterol Disturbs calcium homeostasis MHC-II dependent activation of T-lymphocytes	[26, add Sanjay Kalra ref, 25, 24 Sanjay Kalra's paper]
Hepatotoxicity (transaminases>x ULN)	Caspase activation and apoptosis ↓Coenzyme Q ↑Oxidative stress	[27]
Nephrotoxicity (proteinuria)	Impairs prenylation of proteins critical to receptor mediated endocytosis→Proteinuria	[28]
Rare adverse effects Peripheral neuropathy Memory loss Sleep disturbances Erectile dysfunction	↓Coenzyme Q10 ↓NO availability	[29]

↑: Increase, ↓: Decrease, F-PP: Farnesyl pyrophosphate, GG-PP: Geranylgeranyl pyrophosphate, MHC-II: Major histocompatibility complex II, ULN: Upper limit of normal, NO: Nitric oxide, CK: Creatinine kinase

How to Identify Statin Intolerance

Both statin-induced elevation of CK levels (defined as >10 times the Upper Limit of Normal [ULN]) and hepatic transaminases (defined as >3 times the ULN) have been reported as good predictors of serious statin-adverse effects.[9]

Assessment of creatine kinase in statin-induced myopathy

Statin-induced myopathy is a class effect of statins which tends to progress to rhabdomyolysis at higher doses of statins. Myopathy/rhabdomyolysis is usually precipitated when statins are co-prescribed with interacting drugs, including fibrates and the inhibitors and inducers of hepatic microsomal enzymes (cytochrome P450) which included cyclosporine A, azole antifungals, fibrates, niacin, protease inhibitors, macrolide antibiotics, calcium channel blockers, warfarin, and grapefruit juice.[10] Routine CK assessment was not found useful in detecting rare cases of myopathy in patients who were on the standard statin doses.[11] Statin product information mentions that patients who experienced any new or unexplained muscle pain or weakness must report to their physician and recommended CK assessment in these patients [Figure 1]. In addition, patients with muscle weakness or bilateral proximal muscle pain, excluding other known causes have also been recommended to have their CK assessed. Patients with CK level >10 times the ULN most likely suffer from myopathy and have brown discoloration of urine, which serves as an indicator of overall elevation of myoglobin in the blood. These patients with myopathy have elevated levels of transaminases which normalise on improvement of myopathy. With increase in awareness of drug interactions, statin intolerance could be prevented [Table 2].

Table 2: Important statin drug interactions causing statin intolerance

Name of statin	Metabolism	Drug interaction increasing risk of myopathy[1]
Lovastatin	Mainly CYP3A4	Potent inhibitor of CYP3A4[2]
Simvastatin	Mainly CYP3A4	Potent inhibitor of CYP3A4
Pravastatin	Sulphation, biliary, and urinary excretion	
Fluvastatin	CYP2C9 (some CYP2C8)	Inhibitors of CYP2C9
Atorvastatin	CYP3A4	Potent inhibitor of CYP3A4
Rosuvastatin	Minimal metabolism (via CYP2CP and some CYPC 19)	
Pitavastatin	Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation and biliary excretion	Unclear

[1]With all statins, the risk of myopathy also increases with concomitant use of ciclosporin and gemfibrozil, and possibly other fibrates; prescribing information provides further details and interaction, [2]Including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, nefazodone, HIV protease inhibitors, and regular ingestion of grapefruit juice,[30] HIV: Human immunodeficiency virus

Assessment of hepatic transaminases

Product information of statins mentions the baseline measurement of hepatic enzymes such as ALT (Alanine aminotransferase) and AST (aspartate aminotransferase) and forbids use of statins in active liver diseases.[12] Therefore, patients with baseline liver abnormalities and active disease should refrain from using statins. Generally, at a clinical dose of statins, there is rare (<1%) elevation of hepatic enzymes but at higher doses the level of hepatic enzyme increases with differing intensity depending on the type of statin.

Routine assessment of hepatic transaminases is no longer required for simvastatin, pravastatin, or lovastatin up to

Table 3: Effects of statin withdrawal

Parameters	Negative effects	References
NO	Short-term atorvastatin (10 mg/kg, BW) withdrawal in animal study cause rebound phenomenon and impairment of NO bioavailability Statin withdrawal restores isoprenoids→↑ active Rho protein and ↓NO production	[31]
Endothelium	Impairment of FMD of the brachial artery after discontinuation of atorvastatin (80 mg/day)	[32]
Inflammatory markers	Changes in inflammatory markers such as CRP, IL or MMP have been observed	[33]
C-reactive protein	↑CRP levels in patients with unstable angina pectoris undergoing coronary stenting including patient with acute phase MI	[34]
VCAM-1	Discontinuation of 12 week atorvastatin treatment resulted in a significant elevation of VCAM-1	[34]
MCP-1	Rac protein undergoes a transient "overshoot" translocation back to the membranes→↑ membrane Rac content rapidly→ Rac mediated ROS generation	[35]
PPAR	Atherosclerotic plaque regression observed with combined use of atorvastatin and PPARγ agonists was abolished	[36]
LFA-1	Statins bind LFA-1 receptor covalently inhibiting binding of monocytes and lymphocytes to the adhesion molecules in artery wall, and removal of statin therapy removes this protective effect	[37]
Hemostasis	Significant reduction of plasma tPA within three days of discontinuation of atorvastatin (10 mg/day) Patient with stable CHD showed 3-fold ↑ in thrombotic vascular events after stopping simvastatin therapy	[38]
AT1 signalling	Acute withdrawal of statin may result in the activation of MAPK and expression of AT1 receptor, and MAPK activation in VSMC causes vascular dysfunction	[39]

Withdrawal of statin therapy cast negative effects (Jasinska-Stroschein *et al*., 2011), ↑: Increase, ↓: Decrease, AT-1: Angiotensin II type 1 receptor, CHD: Coronary heart disease, CRP: C-reactive protein, eNOS: Endothelial nitric-oxide synthase, FMD: Flow mediated dilation, IL: Interleukin, LFA-1: Lymphocyte function-associated receptor, MAPK: Mitogen activated protein kinase, MCP: Monocyte chemoattractant protein, MMP: Matrix metalloproteinases, NO: Nitric oxide, tPA: Tissue plasminogen activator, VCAM1: Vascular cell adhesion molecule

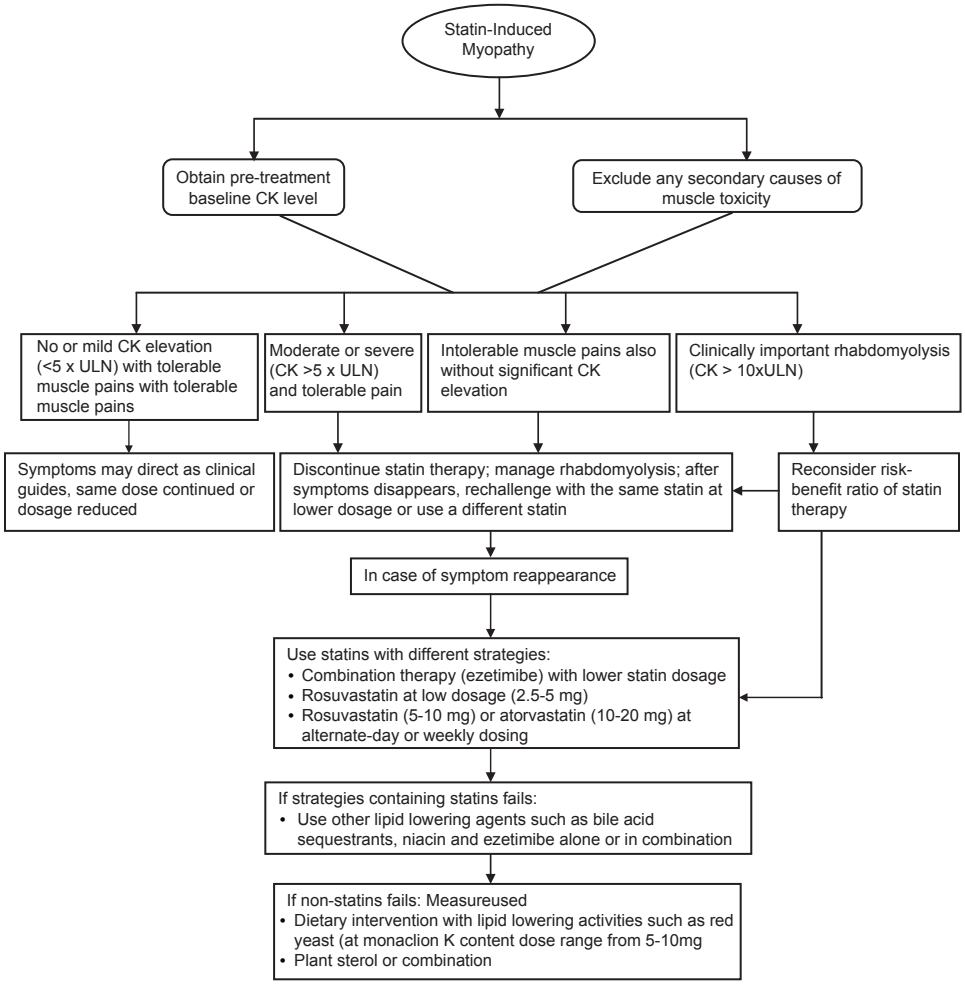

Figure 1: Statin-induce myopathy management

40 mg/day but is recommended for other statins and for higher doses of statins. If ALT or AST levels are >3 times the ULN in an asymptomatic patient with other liver abnormalities, the liver function test should be done within

a week and statins must be stopped temporarily if ALT level did not fall to the normal level.[12] In 2006, the Liver Expert Panel reported that they did not find any proof that statins caused life-threatening liver damage and elevation of hepatic enzymes reversed after stopping statin. The panel did not recommend routine evaluation but suggested repetition of the test in case the transaminases are >3 times ULN and further evaluation if it remains elevated. The statins should be discontinued only in the presence of any objective liver injury.[13]

Management of Statin Intolerance

The first step in the strategy to manage statin intolerance is to rule out extraneous factors that may increase the risk of myopathy/rhabdomyolysis or elevate hepatic transaminases. The National Lipid Association Statin Safety Task Force has prescribed guidelines to manage statin intolerance [Figure 1].

Other strategies used to manage statin intolerance are switching therapy, alternate day dosing, non-statin lipid-lowering drugs, lipid lowering nutraceuticals, and specific pharmacotherapies which are detailed below.

Switching therapy

This strategy of switching therapy is effective in only some patients since the criteria to select the new statins are not clearly delineated.[14,15] Switching from 1) Mild to high lipophilic statin 2) from cytochrome P450 metabolised to non-cytochrome P450 metabolised statin, and 3) to a lower dosage of a more potent statin have been utilised. A prospective, open-label pilot study evaluated the effectiveness and safety profile of rosuvastatin (newer and a highly potent non-cytochrome P450 metabolised statin) at 5 and 10 mg/day doses in patients with primary high LDL-C (mean, 177 mg/dL) and intolerance to other statins due to myalgia.[16]

In moderately high risk patient 5 mg/day rosuvastatin was prescribed and 10 mg/day was prescribed to high or very high risk patients. It was noted after 36 weeks that 5 mg/day rosuvastatin dose reduced LDL-C by 42% and 10 mg/day by 39%. Only one patient who was receiving 10 mg/day rosuvastatin dose discontinued rosuvastatin treatment due to unilateral muscular pain after 4 weeks with no significant elevation in hepatic enzymes.

Alternate day dosing

Statins with longer half-life maintain lipid lowering effect over a longer period of time, enabling alternate day dosing strategy with statin. Atorvastatin with a mean half-life of 14 hrs is metabolised into two active metabolites-orthohydroxy and parahydroxy forms. Both these active metabolites contribute to 70% activity of atorvastatin and have a half-life of 20 to 30 hrs.[17] This pharmacokinetic parameter of atorvastatin makes it suitable for an alternate-day dosage regimen and continues its lipid lowering activity for considerably a longer period of time. Rosuvastatin, a third generation statin, possess a long half-life period of around 19hrs. Two patients who developed intolerance to daily atorvastatin therapy, due to myalgia, were subsequently treated with rosuvastatin (at a dosage of 2.5 mg and 5 mg) on 1st, 3rd, and 5th days of the week, respectively. At both the doses, the level of LDL-C decreased by 38% and 20%, respectively with the resolution of adverse effects after six weeks of treatment.[18] In 2008, Gadarla *et al*., reported use of rosuvastatin (5 and 10 mg), two-times a week (on the first and fourth day of the week) for a period longer than three weeks in patients aged 62-70 years who developed myopathy due to other lipid-lowering therapy.[19] The rosuvastatin dosage regimen was well accepted by 80% of the patients with significant 26% LDL-C reduction from the baseline. In another study, eight patients who were intolerant to daily statin responded well with once-weekly dosage of rosuvastatin (5-20 mg) and reported a mean LDL-C reduction of 29%.[20] The apparent reasons for weekly statin regimen tolerance could be due to either lowering of overall plasma concentration of statins or psychological reasons. However, this alternate day dosing strategy had certain limitation. First, alternate day statin dose administration causes a lower LDL-C reduction (up to 10-15% less) compared to daily dose regimen in high-risk patients. However, this LDL-C reduction was much lower than the ideal LDL-C target set for each high-risk patient. Second, alternate-day dosing strategy has not been established through clinical trials. Thus alternate day dosing strategy should be used only as a secondary option in specific high-risk patients who are intolerant to lower statin dosage.

Non statin lipid-lowering drugs

Non-statin lipid lowering drugs include a bile acid sequestrant (colesevelam), an intestinal cholesterol absorption inhibitor (ezetimibe), fibrates, and niacin which may be either used alone or in combination. These drugs have been considered in cases of unmanaged statin intolerance. Co-administration of ezetimibe and bile acid sequestrants (colesevelam, colestipol, or cholestyramine) yields additional reduction of LDL-C levels without any adverse effects in comparison to stable bile acid sequestrant regimen alone. Addition of ezetimibe to nicotinic acid lowers LDL-C levels without modifying nicotinic acid-induced increase of HDL-C. The triple therapy i.e. bile acid sequestrant, statin, and ezetimibe or nicotinic acid further reduces LDL-C levels. However, no clinical outcome studies with these combinations have been performed. Functional food containing phytosterols or plant sterol containing

tablets have been reported to reduce LDL-C levels up to 5-10% in patients taking a stable dose of a statin. This combination of plant sterol and statins was have been reported as well tolerated and safe.[21,22] Since no clinical trials with combination of plant sterols and other lipid-lowering drugs have been established for CVD outcomes, their efficacy in CVD risk reduction remains speculative.

Use of lipid lowering nutraceuticals

Various dietary interventions, including foods low in saturated fat and high in viscous fibers (e.g., oats and barley), plant sterols, vegetable protein foods (soy), and nuts (e.g., almonds) have been used in patients who cannot tolerate statins. The efficacy of these dietary interventions was further strengthened by addition of nutraceuticals such as red yeast.[23] In 2003, Jenkins and colleagues reported that dietary portfolio of cholesterol-lowering foods caused cholesterol lowering effect comparable to a statin. But due to its limitation of palatability, dietary supplements were used as an alternative option.[24] Chinese red yeast rice is a dietary supplement made by fermenting the yeast, *Monascus purpureus,* over rice. Monascus yeast produces a family of substances called monacolins capable of inhibiting the enzyme HMG-CoA reductase and also contains unsaturated fatty acids and phytosterols. Red yeast rice offers only modest LDL-C lowering (up to 20%) and has been prescribed to only low-risk individuals or in whom LDL-C level is not far from the target.[25]

Specific Pharmacotherapies

Presently, there is a lack of consensus on the use of specific pharmacotherapy for statin-induced myopathy. Coenzyme Q10 (CoQ10) deficiency has been correlated with the development of myopathy. Various studies have reported significant improvement in statin-induced adverse effects-myopathy, myalgia, peripheral neuropathy, fatigue, dyspnoea, and memory loss if coenzyme Q10 was given as a co-therapy with statins.[26-30] In 2009, Kalra *et al*.,[5] reported that coenzyme Q10 (200 mg/day) supplementation in statin-treated patients would help in preventing statin-induced adverse effects, leading to low statin intolerance and maximal benefits of statin.

Vitamin deficiency has been associated with myalgia and poor muscle function and its supplementation have shown ameliorative effects in statin induced myopathy. A recent trial has shown that 92% of patients become myalgia free after three months of vitamin D supplementation.[31]

Conclusion

In recent years, increasing complaints of intolerance to statins have considerably impacted outcomes, especially in high-risk patients. Furthermore, several studies have reported negative consequences of acute statin withdrawal on cardiac patients, especially the patients with ACS and stroke. Increased understanding of statin-induced adverse-effects and awareness of clinical implications of acute statin withdrawal has discouraged patients from abrupt discontinuation of statin therapy. Statin intolerance has been effectively managed either by the use of alternate-day statin regimen with longer half lives like atorvastatin and rosuvastatin, combination of statins with non-statins, dietary interventions, or by specific pharmacotherapies.

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