Management of hyperlipidemia in patients with statin intolerance

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Why statins?
Statins, or HMG CoA reductase inhibitors, are among the most commonly prescribed drugs in the world today. These medications have been repeatedly shown to reduce low-density lipoprotein cholesterol (LDL-C) by 19-60% depending on the statin and dose used.1,2 In patients with existing coronary artery disease (CAD), statins have been shown to decrease incidence of non-fatal myocardial infarction,3 incidence of stroke,4 mortality from CAD,1 and all-cause mortality.1 These same benefits have also been found in patients without CAD but with cardiovascular risk factors including diabetes.5 For this reason, statins are considered to be first line in the management of hyperlipidemia in patients who, according to the Framingham risk calculator, are at high risk for coronary artery disease as well as those at medium or low risk who have failed to meet lipid targets with lifestyle modification.6

Adverse effects and statin intolerance
Despite the significant effect of these drugs on mortality and morbidity, statins, like all drugs, have adverse effects. However, the HMG CoA reductase inhibitors generally have a favorable side-effect profile.5 The most common adverse effects and the primary contributors to statin-intolerance are muscle symptoms and creatine kinase (CK) elevations.6

There are many definitions in the literature regarding the spectrum of statin-induced muscle symptoms. One commonly used set of definitions, from the National Lipid Association (NLA) Statin Safety Assessment Task Force, is as follows: (1) myalgia: muscle pain or soreness, (2) myopathy: myalgias, weakness or cramps and CK >10x the upper limit of normal, and (3) rhabdomyolysis: CK >10 000 IU/L or CK >10X the upper limit of normal plus elevation of serum creatinine or need for intravenous hydration.6 The rate of statin-induced myalgia in observational studies is 10-15% while the rate of myopathy is 0.1-0.2%.7 Meanwhile, rhabdomyolysis is even less common and has been seen mainly when statins have been used in combination with fibrates or cyclosporine.7

In the case of myopathy or rhabdomyolysis, the NLA task force recommends discontinuing the statin. Restarting the statin after these events is controversial; nevertheless, there is a general consensus that the clinician must weigh the risks and benefits before making this decision.5 However, most patients on a statin presenting with muscle symptoms will fit the definition of myalgia. If these myalgias are intolerable, the NLA recommends discontinuing the statin. Meanwhile, if the myalgias are tolerable, the statin should be continued at the same or lower dose or a statin holiday may be given.6

When patients have recurrent myalgias after taking a reduced dose of their statin or after restarting their statin subsequent to a drug holiday, alternative approaches to lipid management are required. This presents a challenge to physicians managing lipids in patients with or at risk for vascular disease because non-statin lipid lowering medications have not been shown to have the same robust effect on morbidity and mortality as statins and present their own set of adverse effects.8 In the recent literature, alternative statin regimens aimed at those who have previously been intolerant to the medications have been proposed. Three such regimens are reviewed below.

Modified statin therapy

Switching the statin

According to the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, an observational trial of nearly 8000 unselected patients using statins in France, high dose fluvastatin (80mg) is associated with the lowest rate of muscular symptoms (5.1%) when compared to high dose pravastatin (10.9%), atorvastatin (14.9%) and simvastatin (18.2%).9 This had led many clinicians to recommend a trial of switching patients intolerant to their current statin to fluvastatin.5,10 While this statin is considered to be lower in potency than others,11 a recent trial showed fluvastatin 60mg reduced LDL-C by 31% and significantly reduced atherosclerotic plaque volume in patients with CAD.12 Furthermore, fluvastatin XL has been demonstrated to be well-tolerated among statin-intolerant patients.13

Alternate day and weekly statin dosing

Given that atorvastatin and rosuvastatin have long half-lives, alternate day dosing of these statins has recently been attempted in statin intolerant patients to reduce the risk of adverse muscular effects. While tolerated by 72% of patients, a dose of 2.5-10mg of rosuvastatin every other day in previously statin-intolerant patients has been found to reduce LDL-C by 34%.14 Similarly, a 23% reduction in LDL-C has been reported in 74% of previously intolerant patients now receiving once weekly rosuvastatin.15 However, these studies have not yet addressed whether alternate day or weekly statin dosing has the same effect on vascular event rates and mortality rates that daily dosing does.

Statin and ezetimibe combination

Ezetimibe is a cholesterol absorption inhibitor that has received a significant amount of attention since a double-
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blind study showed similar LDL-C reductions between ezetimibe (10mg/day) combined with atorvastatin 10mg/day and atorvastatin 80mg/day alone. However, even with the lower dose of statin in this short trial, the combination therapy did not have a lower rate of musculoskeletal side-effects and CK elevations than the high dose statin therapy. Further, in a more recent long-term (48 week) trial comparing the safety of ezetimibe combined with simvastatin and simvastatin alone, there was no difference in musculoskeletal adverse-effects or CK levels. However, a recent randomized controlled trial has revealed that the combination of fluvastatin and ezetimibe is well-tolerated in statin-intolerant patients.

Non-statin therapy

When patients with hyperlipidemia can not tolerate any form of statin therapy, non-statin alternatives can be employed. These include fibrates, niacin, bile acid absorption inhibitors, ezetimibe, and potentially omega-3 fatty acids.

Niacin

Niacin is perhaps the most potent of these drugs and has been shown to raise high-density lipoprotein cholesterol (HDL-C) and lower LDL-C as well as, in older studies, to reduce cardiovascular events and mortality. However, the side effects, which include cutaneous flushing and gastrointestinal upset, have limited its use. Recently, there has been renewed interest in niacin, including ongoing trials evaluating mortality outcomes and investigation into attenuation of these side-effects.

Fibrates

Fibrates are well studied and have been found to significantly reduce triglyceride levels and increase HDL-C levels while having a smaller effect in reducing LDL-C levels. In terms of outcomes, two recent meta-analyses found that while currently available fibrates significantly reduce the odds of non-fatal myocardial infarction (MI), they had no effect on cardiovascular mortality, rate of stroke, or all-cause mortality. Adverse effects in both of these trials were primarily gastrointestinal, while myalgias occurred at the same rate as in the placebo groups.

Bile acid and cholesterol absorption inhibitors

Bile acid absorption inhibitors, similar to niacin, have been studied mostly in older, pre-statin era trials. In these trials, cholestyramine, a first generation bile acid sequestrant, mainly reduced LDL-C levels as well as cardiovascular events and mortality. However, again like niacin, these drugs have been limited by their gastrointestinal side-effects such as constipation. A newer bile acid sequestrant, colesevelam, is tolerated much better by patients and delivers similar LDL-C reductions as the older medications, but no outcome data are available to this point. Ezetimibe alone has been shown to deliver modest reductions in LDL-C and, in two trials, has been well tolerated by patients intolerant to statins. However, there is currently no evidence that this drug influences cardiovascular event or mortality rates.

Omega-3 fatty acids

Recently, there has been some interest in the role of omega-3 fatty acids in cardiovascular disease. A large (18000 patients), randomized trial in Japan found that omega-3 supplementation (eicosapentaenoic acid 1800mg/day) significantly reduced triglyceride levels as well as non-fatal coronary events. However, we await replication of these findings in randomized double-blind, placebo-controlled settings. Adverse effects have included gastrointestinal disturbance, skin reactions, and hemorrhage.

Conclusion

Statins have been widely studied and there is robust evidence supporting their lipid lowering properties and beneficial effects on cardiovascular morbidity and mortality. These medications are generally safe and serious adverse events are rare. However, the most common side-effects that lead to statin-intolerance are muscle symptoms. When patients are unable to tolerate their current statin, there is some evidence to support switching to fluvastatin, less frequent statin dosing, or combination with ezetimibe. However, it is currently unclear if the mortality benefits associated with statins carry over to these modified statin therapies. If patients are unable to tolerate any form of statin therapy, non-statin medications may be used. Unfortunately, many of them are not well tolerated and are still awaiting convincing data for cardiovascular event benefit. Further investigation into the efficacy on cardiovascular outcomes in alternate statin and non-statin regimens in statin-intolerant patients is required. While medications for hyperlipidemia may be tailored according to adverse effects experienced by patients as well as their particular lipid profile, it is important to continually emphasize the need for lifestyle modification including diet and exercise in the management of hyperlipidemia.

References


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