State-of-the-Art Article

Statin intolerance

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Abstract

Statins are the cornerstone of therapy for reducing low density lipoprotein (LDL), and subsequently, for reducing cardiovascular morbidity and mortality in high-risk patients. However, although adherence to statins improves morbidity and mortality[1], it remains suboptimal.[2] One of the most important causes of non-adherence is the so-called statin intolerance, mainly because of muscle-related symptoms. These symptoms most often consist of myalgia unaccompanied by significant creatinine kinase (CK) elevations. Less often, myositis (elevated CK >10 times the upper limit of normal) or rhabdomyolysis (CK level >10,000 IU/L or accompanied by significant elevation in creatinine level) develops.

The initial step in patients with adverse symptoms during the course of statin therapy is to identify those for whom true statin intolerance is unlikely, since most of these patients would probably be capable of tolerating adequate statin therapy. In patients with statin intolerance, an altered dosing regimen of very low doses of statins should be attempted, and if tolerated, should gradually be increased to achieve the highest tolerable doses. In addition, other non-statin lipid-lowering drugs may be needed, either in combination with statins, or alone, if statins are not tolerated at all.

Recently, some newer non-statin molecules like Mipomersen and proprotein convertase subtilisin/kexin 9 (PCSK-9) inhibitors, showed encouraging results. Strict control of other risk factors can aid in reducing cardiovascular risk if attaining lipid treatment goals proves difficult.

Keywords

- Statin
- Statin intolerance
- Muscle side effects
- Myalgia
- Low-dose statin therapy

Introduction

Statins effectively decrease cardiovascular risk, and cholesterol lowering with statins has become a cornerstone of cardiovascular disease prevention for a wide range of patients.[3] Despite this, adequate use of statins is limited by adverse symptoms in many patients,[4-6] which leads to statin discontinuation in some patients, and low adherence to therapy in others. The issue of statin intolerance is, therefore, of great clinical importance. There is significant uncertainty regarding the actual incidence, and there is insufficient knowledge concerning the best therapeutic approaches to the problem. Most cases of statin intolerance are related to muscle complaints,[7-9] with increased liver or muscle enzyme[10];Various

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neurological symptoms[11] and other problems are much less frequent. The glycemic effects of statins are occasionally included as a symptom of statin intolerance; however, they are undesired side effects rather than serious findings necessitating discontinuation of therapy in individual cases. Moreover, the diabetogenic effects of statins are generally overestimated. It should be noted that all of the mentioned symptoms can stem from a number of different causes and are often unrelated to actual statin use. However, even among patients with true statin-related symptoms, many can tolerate lower doses of the same statin, or perhaps a different statin. Establishing a diagnosis of statin intolerance is thereby less straightforward than it appears, and an adequate therapeutic approach is more complex than simple discontinuation of statin therapy. As a result of these complexities, statin intolerance is currently gaining increased attention and several guidelines[12,13] and review papers[14-17] have recently been published, thereby providing an in-depth discussion of this complicated, and often controversial, topic.

Definition

As the name suggests, statin intolerance occurs when a patient is unable to tolerate a statin, either because of the development of a side effect or because of evidence on a blood test that certain markers of liver function or muscle function (creatinine kinase) are sufficiently abnormal.[18] The intolerance can be either partial (i.e., only some statins at some doses) or complete (i.e., all statins at any dose). The most common presentation of statin intolerance is muscle aches, pains, weakness, or cramps, often called myalgias; these can occur in up to 15% of treated patients. The clinical trials by and large indicate that approximately 5% and 10% of patients are statin intolerant.[19] In most instances, the symptoms are mild and are rarely associated with muscle inflammation (myositis) and markers of muscle injury (creatinine kinase).[18] Moreover, the symptoms are completely reversible shortly after the statin discontinuation. Serious muscle damage or rhabdomyolysis associated with statin treatment is extremely rare, for instance, occurring in 1 in 23 million individuals with prescriptions for atorvastatin. Mild to moderate increases in creatinine kinase may occasionally be seen in patients taking statins who have no muscle-related side effects, but this should not be grounds to stop statin therapy. It is theorized that some of the muscle side effects may be related to the effects of statins on energy metabolism[18] or that the symptoms are attributable to reduced levels of coenzyme Q10 in muscles.

What are the risk factors that can cause statin intolerance?

Table 1 lists some factors that have been associated with an increased risk of developing statin-related intolerance, primarily myalgias.

Table 1: Factors associated with increased risk of statin intolerance

- History of muscular symptoms with other lipid-lowering therapies
- History of unexplained muscular symptoms
- History of unexplained creatinine kinase elevation
- Family history of muscular symptoms with lipid-lowering therapy
- Strenuous exercise
- Hypothyroidism
- Vitamin D deficiency
- Drug interactions (gemfibrozil, macrolides, azole antifungals, verapamil, amiodarone, protease inhibitors, cyclosporine)
- Advanced age
- Female gender
- Low body mass index
- Alcohol abuse

The American College of Cardiology has recently developed an ACC Statin Intolerance App to aid clinicians in evaluating and managing patients who report muscle symptoms while on a statin (available at http://www.acc.org/StatinIntoleranceApp).

Potential adverse effects of statins

These are highlighted in Table 2

Table 2: Potential Adverse Effects of Statins

1. Adverse effects for which there is good supportive evidence:

Myopathy (muscle aches/cramps, myositis, rhabdomyolysis)
Increase in liver function enzymes
New-onset diabetes mellitus

2. Adverse effects for which there is little or no supportive evidence:

Cancer
Intracerebral hemorrhage (bleeding stroke)
Cognitive decline (Alzheimer disease)
Lung disease
Erectile dysfunction
Fatigue, headaches, or dizziness
Psychiatric illness
Cataracts
Rheumatoid arthritis
Gastrointestinal upset, abdominal cramping
Permanent liver or kidney damage

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.[13]

Assessment of creatinine kinase in statin-induced myopathy

Statin-induced myopathy is a class effect of statins that 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 include cyclosporine A, azole antifungals, fibrates, niacin, protease inhibitors, macrolide antibiotics, calcium channel blockers, warfarin, and grapefruit juice. Routine CK assessment was not found useful in detecting rare cases of myopathy in patients who were on the standard statin doses. Patients with muscle weakness or bilateral proximal muscle pain, excluding other known causes have 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 that normalise on improvement of myopathy. With increased awareness of drug interactions, statin intolerance could be prevented.

Assessment of hepatic transaminases

Product information of statins mentions the baseline measurement of hepatic enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and avoids use of statins in active liver diseases. Therefore, patients with baseline liver abnormalities and active disease should refrain from using statins. At a clinical dose of statins, there is generally 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 a week, and statins must be stopped temporarily if ALT level does not fall to the normal level. In 2006, the Liver Expert Panel did not find any evidence 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.

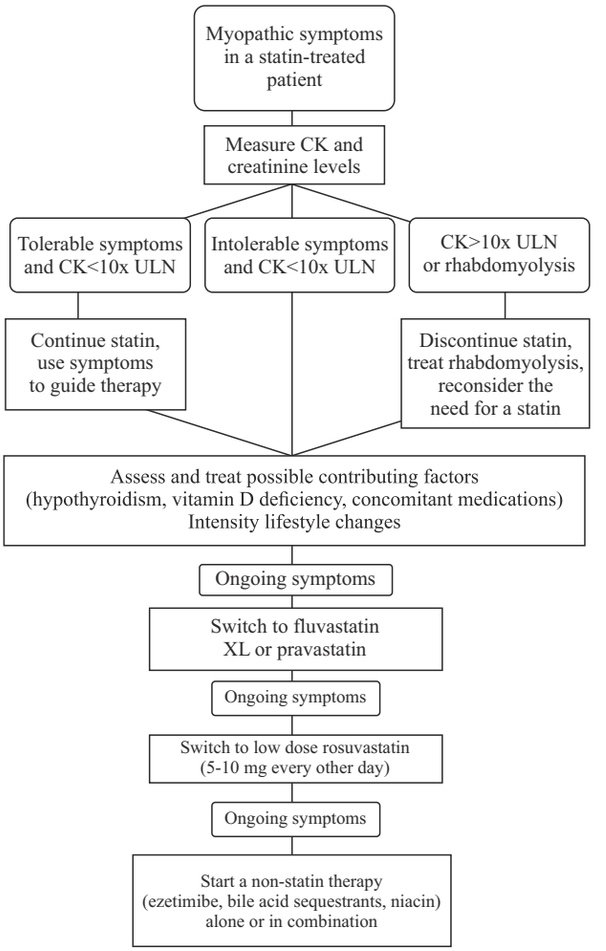
Evaluation of Statin Intolerance

Due to the exclusion of subjects with a history of muscular disorders or at risk for myalgia, the real frequency of statin-induced myotoxicity has been underestimated in the randomized clinical trials.[20-21] In contrast, in the everyday clinical practice, a relevant number of subjects experiencing myalgia during statin therapy is observed; thus, the real clinical impact of muscular side effects induced by statins has been specifically evaluated in two studies. The Prediction of Muscular Risk in Observational conditions (PRIMO) study was an observational survey of muscular symptoms in an unselected population of hyperlipidemic subjects taking high-dose statins.[22] This study revealed that mild to moderate muscular symptoms occurred more frequently (10.5%) in patients treated with high-dose statins than established in randomized clinical trials and that the type of statin used was an independent predictor of muscular symptoms, with extended-release fluvastatin associated with the lowest occurrence (5.1%) and simvastatin with the highest risk (18.2%).[22] The median time of onset for muscular symptoms was 1 month after statin therapy initiation or titration to a high dosage[22]; 57% of the patients experiencing muscular symptoms were switched to another lipid-lowering therapy (61% to another statin, 28% to a fibrate), or to a lower dosage of the same statin (17%), while 20% of the patients completely discontinued statin therapy.[22] This study observed that the occurrence of muscular symptoms in subjects taking high-dose statin negatively impacts the everyday life, as a high number of subjects (25%) reported a continuous muscular pain and 39% needed an analgesic for pain relief.[22] These findings, confirmed by an observational survey conducted in a large unselected population of hypercholesterolemic subjects taking statins,[23] may explain why poor patient compliance represents a major issue for statin-treated subjects. The Effects of Statins on Skeletal Muscle Function and Performance (STOMP) study evaluated the impact of high dose statin therapy (atorvastatin, 80 mg) for 6 months in healthy, statin-naive subjects.[24] This study revealed that atorvastatin significantly increased the frequency of myalgia compared with placebo (9.4% vs. 4.6%)[23]; CK levels increased also in asymptomatic atorvastatin-treated subjects (although none exceeded the 10× ULN), suggesting that high dose statin may induce a low-grade muscle injury, although increased CK did not impact skeletal muscle function.[23] More atorvastatin-treated subjects at least doubled their baseline CK levels; however, these levels were not associated with deterioration of muscle function.[25] Thus, this confirmed that increased CK does not suggest statin-induced muscle injury. Finally, subjects with myalgia tended to be older, and almost 60% were women.

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 (Fig. 1). Other strategies used to manage statin intolerance are switching therapy, alternate day dosing, non-statin lipid-lowering drugs, and specific pharmacotherapies.

Proposed alogorithm for the management of statin-associated myopathy.



Rafael Bitzur et al. Dia Care 2013;36:5325-5330

Figure 1: Statin-induced myopathy management

Switching therapy

This strategy of switching therapy is effective only in some patients since the criteria to select the new statins are not clearly delineated.[26,27] Switching from mild to high lipophilic statin, from cytochrome P450 metabolised to non-cytochrome P450 metabolised statin, and 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.[28] In moderately high risk patient, 5 mg/day rosuvastatin was prescribed and 10 mg/day was prescribed to high or very high risk patients. After 36 weeks, it was noted that 5 mg/day rosuvastatin dose reduced LDL-C by 42% and 10 mg/day rosuvastatin dose reduced LDL-C 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 h 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 20–30 h.[29] 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 approximately 19 h. 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 the first, third, and fifth 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.[30] In 2008, Gadarla et al. reported use of rosuvastatin (5 mg 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.[31] 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%.[32] The apparent reasons for weekly statin regimen tolerance may be because of 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

Other lipid-lowering drugs may be needed to achieve appropriate targets, either in combination with statins, or alone, if statins are not tolerated at all. A combination of these drugs and low-dose statin therapy can provide reductions in LDL-C similar to those obtained with high doses of statins.

Ezetimibe decreases LDL-C by 15–20% (either in combination with statins or as monotherapy) and is widely used in patients with statin intolerance. Ezetimibe is well tolerated, but the evidence of cardiovascular benefit is limited to one trial that demonstrated a modest 6% reduction of cardiovascular events.[33]

Fibrates are primarily used to lower triglycerides and increase high-density cholesterol; they also decrease LDL-C levels, but to a lesser extent. The effect on LDL-C is more pronounced in patients with hypertriglyceridemia. Accordingly, the reduction of cardiovascular risk with fibrates is only 10% in unselected patient population, but is substantially greater (>30%) in patients with hypertriglyceridemia.[34] Thus, fibrates represent a reasonable option in these patients. However, caution must be exercised when combining fibrates with statins, as the combination may increase the risk of myalgia.

Bile acid sequestrants (resins) provide LDL-C reduction that is comparable to that observed with ezetimibe, and they have been proven to reduce cardiovascular events. Resins are safe, but poorly tolerated, due to gastrointestinal side effects.

The recently developed colesevelam has fewer side effects and better patient compliance.

Niacin is similar to fibrates relative to its effect on blood lipids, but its use in clinical practice has dropped substantially after two clinical-endpoint trials failed to demonstrate cardiovascular benefits of niacin therapy.[35,36]

Mipomersen

Visser and Stroes have now presented Phase II data from a randomized double-blind placebo-controlled trial of mipomersen in high-risk patients who are unable to take statins.[37] Mipomersen is a novel antisense oligonucleotide that inhibits the synthesis of apolipoprotein B-100 (apoB-100) and is a long-lasting injectable drug that is metabolized both hepatically and renally. ApoB-100 is the primary structural apolipoprotein of LDL particles and is involved in secretion of very low-density lipoprotein (VLDL) and delivery of LDL to tissues. By inhibiting synthesis of this integral protein in cholesterol secretion and delivery, mipomersen can dramatically reduce the concentration of circulating LDL, making this drug a highly appealing option for patients who are unable to tolerate statins. The first human studies of this compound in 36 volunteers with mild dyslipidaemia indicated reduction in apoB by a maximum of 50% (P ¼ 0.002), which corresponded to an LDL reduction of 35% (P ¼ 0.001), with effects being maintained even 3 months after the last dose.[38] Doses in this trial ranged from 50 to 400 mg and were administered mostly subcutaneously (initial loading dose, weeks 2, 3, and 4) except for one dose which was given intravenously (week 1).

Lomitapide inhibits the lipid transfer activity of MTP, thus inhibiting the assembly of intestinal chylomicrons and hepatic VLDL and results in reduced secretion of these lipoproteins into the circulation. Lomitapide was shown to be effective in reducing LDL-C levels in patients with moderate hypercholesterolemia in monotherapy as well as in combination with ezetimibe.[39]

PCSK9 inhibitors are a novel class of lipid-lowering drugs; they were approved quite recently in the USA and Europe. They reduce LDL-C levels by approximately 50%. Meta-analyses of phase 2 and 3 trials demonstrated a >50% reduction of cardiovascular events with evolocumab and alirocumab.[40,41] In the ODYSSEY ALTERNATIVE study[42], investigational PCKS9 monoclonal antibody, alirocumab, produced significantly greater LDL-C reductions in statin-intolerant patients with very high baseline LDL-C levels compared with ezetimibe, a drug often used in this population. The recently presented GAUSS-3 trial[43] in ACC-2016 demonstrates that in patients with statin-induced muscle-related adverse events, the use of evolocumab resulted in a significantly greater reduction in LDL-C levels after 24 weeks, compared with ezetimibe (Fig 2). Statin intolerance is one of the approved indications for use of PCSK9 inhibitors.

GAUSS-2 and ODYSSEY ALTERNATIVE

PCSK9 Inhibitors Well Tolerated by Statin-intolerant Patients

Trail	N	Drug	Patients Completing Treatment, %
GAUSS-2[(a)]	307	Evolocumab	96
ODYSSEY ALTERNATIVE[(b)]	314	Alirocumab	95

a. Stroes E,et al. *JAm Coll Cardiol. 2014;63:2541-2548*.
b. Moriarty PM, et al. *J Clin Lipidol. 2014;8:554-561*

Figure 2: PCSK 9 inhibitors in Statin intolerance

Specific Pharmacotherapies

There is a currently 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.[44-46] In 2009, Kalra et al.[47] 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 D 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.[48]

Lipid-Lowering Nutraceuticals

Nutraceuticals play an important role in cardiovascular prevention in patients with dyslipidemia. Many scientific studies support the use of these substances alone or associated with other drugs in clinical practice. Specifically, monacolins, berberine, policosanol, and gamma-oryzanol could significantly reduce cholesterolemia. However, there is still an insufficient number of studies demonstrating morbidity and mortality outcomes of nutraceuticals, nor is there sufficient data on the use of nutraceuticals in different types of patients, on tolerability, safety, target population, modality, and duration of use present in the literature. Chinese red yeast rice is a dietary supplement containing monacolins, unsaturated fatty acids, and phytosterols capable of lowering low-density lipoprotein (LDL) cholesterol. Few studies have reported on its use in clinical practice or in statin-intolerant patients.[49]

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. 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 non-statin drugs. Newer therapies currently under development, such as mipomersen (an antisense inhibitor of apolipoprotein B), lomitapide (a microsomal transfer protein inhibitor), and PCSK-9 inhibitors, may prove useful in statin intolerant patients.

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