HOSPITAL CHRONICLES 2013, 8(2): 60–70

REVIEW

Dyslipidemia: Treatment in Statin – Intolerant Patients

Ioannis Skoumas, MD

Lipid & Metabolic Syndrome Unit, First Department of Cardiology of Athens University, Ippokratio Hospital, Athens, Greece

KEY WORDS: *statins; myositis; myalgias; creatine kinase; transaminases; drug hepatitis*

Abbreviations
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CK = creatine kinase
CoQ10 = coenzyme Q10
CVD = cardiovascular disease
GGT = gamma-glutamyl transferase
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A
LDL = low density lipoprotein
NNH = number needed to harm
NNT = number needed to treat
SIM = statin-induced myopathy
ULN = upper limit of normal

Correspondence to:
Ioannis Skoumas, MD, First Department of Cardiology, Ippokratio Hospital, Athens, Greece;
e-mail: skoumasj@yahoo.gr

Manuscript received November 2, 2012; revised manuscript received January 28, 2013; Accepted March 12, 2013

ABSTRACT

Statins are the mainstay of lipid-lowering therapy because of their well-established efficacy for reducing cardiovascular disease mortality and morbidity in various high risk populations. However, certain patients cannot avail themselves of these beneficial effects due to intolerance in these agents. Statin-induced myopathy is by far the most common side-effect. A less common side-effect of statin therapy is hepatic toxicity. Intolerance to statins is frequently encountered in clinical practice, mostly due to muscular symptoms and/or elevation of hepatic aminotransferases, which overall constitute approximately two-thirds of reported adverse events during statin therapy. The first step in handling intolerant patients is to rule out any secondary causes of myopathy or liver toxicity. The second step is to determine whether the adverse effects are indeed related to statin therapy by statin dechallenge and rechallenge. Another option is to restart therapy with the same statin at a lower dosage or to switch to another statin with different pathways of metabolism. If the symptoms recur, different approaches should be considered, such as unconventional dosing (every other-day or weekly administration) of statins with longer half-life. Another option in patients who cannot tolerate statins is the use of non-statin lowering drugs, such as ezetimibe, bile acids sequestrants (colesevelam) and fibrates, alone or in combination. Concerning low-risk individuals, the use of herbal supplements effective in reducing LDL cholesterol may be considered.

INTRODUCTION

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the mainstay of lipid-lowering therapy because of their well-established efficacy for reducing cardiovascular disease (CVD) morbidity and mortality in various high risk populations.[1] In general, statin therapy is considered to be safe; however, it may be associated with rare occurrences of serious adverse events.[2] Nevertheless, a significant proportion of subjects taking these drugs may experience some degree of intolerance. In particular, statin-induced myopathy (SIM) is by far the most common side effect. A less common side effect of statin therapy is the increase of serum aminotransferase levels, which is considered the manifestation of hepatic toxicity.[3]

Conflict of Interest: none declared
Author statement: The article is original and has not been published before.

CLINICAL ASPECTS OF STATIN-ASSOCIATED ADVERSE EFFECTS

The incidence of adverse events during statin therapy has been evaluated by several studies. In a meta-analysis of 18 primary and secondary prevention placebo-controlled trials, involving over 70,000 subjects, the number needed to harm (NNH) for any adverse event with statins was 197 and the number needed to treat (NNT) to prevent one cardiovascular event was 27.[4] Thus, treating 1,000 patients would prevent 37 cardiovascular events and cause 5 adverse events. In this analysis, serious adverse events, such as elevated values of creatine kinase (CK), reaching 10 times the upper limit of normal (ULN), or rhabdomyolysis, are rare and have a NNH of 3,400. Rhabdomyolysis alone was extremely rare with an NNH of 7,428. Another meta-analysis of 83,858 patients treated with statins, revealed a low incidence of myositis (0.11%) or rhabdomyolysis (0.016%), with no significant increase in statin-treated compared with placebo-treated patients.[5] However, it must be noted that the SIM in real-world clinical practice is often much higher than that reported in clinical trials. One likely explanation for this discrepancy is the underestimation of the rate of myopathy in clinical trials, because patients at increased risk for statin-induced adverse effects tend to be excluded from the study and the presence of muscle symptoms or increases in CK during the run-in phase of trials may exclude these subjects from randomization.[6] On the other hand, a great number of patients in clinical practices have many other severe comorbidities and may not be as healthy as those enrolled in clinical trials.

To obtain data that are representative of clinical practice, it may be helpful to examine databases from cohort studies. One such cohort study is the Prediction of Muscular Risk in Observational Conditions (PRIMO).[7] In the PRIMO study, over 7,900 hyperlipidemic patients treated with high-dose statin therapy were enrolled in a 12-month, prospective observational follow-up. Muscle symptoms were reported in 11% of patients. This figure has been confirmed by others,[8] and therefore in the real world, SIM may affect 10%–15% of statin users.

The clinical presentation of statin myopathy varies from mild fatigue to rhabdomyolysis requiring hospitalization. The most frequently reported symptoms include myalgia, fatigue, weakness, generalized aching, and low back or proximal muscle pain.[9,10] There have been less frequent complaints of tendon pain and nocturnal muscle cramps.[10] 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.[11]

The relationship between initiation of statin treatment and onset of symptoms is widely variable, as is the time between cessation of statin treatment and the resolution of symptoms. In the PRIMO study the median time of onset of muscle symptoms was 1 month following initiation of statin therapy or titration to a higher dosage. In another study that used 2 large UK primary care databases including a population of about 5 million people with a follow-up period over 10 years, for many patients, it was reported that most SIM cases occurred within the first 12 weeks of statin exposure, although few ones could be seen up to 52 weeks of treatment.[12]

SIM does not appear to be related to statin dosage. In a review of several atorvastatin trials, treatment-related myalgia occurred at a similar rate of 1.4% and 1.5% in subjects receiving 10 or 80 mg of atorvastatin compared with a rate of 0.7% with placebo.[13] A retrospective analysis of safety from the PROVE-IT trial also suggested that statin adverse effects are not related to low density lipoprotein (LDL) level.[14] In fact, muscular and hepatic side effects were found to occur at the same rate across all on-treatment LDL-cholesterol (LDL-C) levels, including very low levels of 40 mg/dL. This phenomenon has been confirmed in a recent meta-analysis comparing different statin doses and on-treatment LDL-C levels.[15] Myopathy in the elderly can produce a much greater functional impairment than in younger patients and this should be taken into account when prescribing lipid-lowering therapies in these patients, particularly when life expectancy is not long enough.

The other statin-associated adverse effect, the hepatic biochemical abnormality, is the asymptomatic elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which appears to be a class effect of statins and is characterized by liver enzyme elevation in the absence of clear hepatoxicity.[3,9] This side effect could be well interpreted according to Hy's rule, which states that serum bilirubin twice the ULN, with ALT more than three times the ULN, with all other causes of liver dysfunction excluded, indicates drug-related hepatotoxicity. This has been also defined as 'transaminitis'. This condition may take several months to develop and is usually transient with full resolution following withdrawal of the drug. The isolated elevations in gamma-glutamyl transferase (GGT) due to statins is rare.[16] The occurrence of aminotransferase elevation during statin therapy ranges from 1%–3%,[17,18] appears to be dose related,[19,20] and may be related to bioavailability. In a recent meta-analysis,[15] the frequency of a persistent elevation of ALT (3 times ULN) for atorvastatin 80 mg and simvastatin 80 mg was up to 5 times compared to atorvastatin 10 mg and simvastatin 20–40 mg (0.2% vs 1%). Hepatocellular injury seen during statin therapy seemed to be an early side effect, occurred on average 4 weeks (range 1 to 8 weeks) after initiation of treatment but resolved within 4 weeks of statin therapy discontinuation.[21]

PATHOPHYSIOLOGY OF STATIN – ASSOCIATED ADVERSE EFFECTS

Although the underlying mechanisms of statin–associated adverse effects have not been determined, several hypotheses have been proposed. Cholesterol plays a key role in cell membrane fluidity, and therefore it has been suggested that cholesterol reduction with statins may perturb the integrity of the plasma membrane of myocytes.[22] Another hypothesis is based on the reduction of ubiquinone or coenzyme Q10 (CoQ10), due to the block of cholesterol synthesis by statins early in its metabolic pathway.[23] A reduction in this coenzyme could result in an abnormal mitochondrial respiratory function due to the key role that plays in the electron transport chain. However, several lines of evidence make these explanations unlikely, because when cholesterol is decreased by inhibiting squalene synthetase, no increase in myotoxicity is observed.[24] On the other hand, human and animal studies have demonstrated that statin treatment may reduce serum CoQ10 levels; however myocyte CoQ10 levels have not been consistently decreased with statin treatment.[25]

Another proposed mechanism of myotoxicity is depletion of isoprenoids that control the rate of myofiber apoptosis.[26] Isoprenoids are lipids produced by HMG-CoA reductase pathway.[27] Isoprenoids are linked to proteins by either farnesylation or geranylgeranylation. According to this theory, statins block the production of farnesyl pyrophosphate and this prevents the prenylation of GTP-binding proteins Ras, Rac, and Rho. There is evidence that reduction of the prenylated forms of these proteins leads to increased cytosolic calcium, which in turn activates a cascade of events leading to the activation of proteolytic enzymes caspase-3 and caspase-9, which have a central role in cell death.[27] The apoptosis theory is supported by studies on vascular smooth muscle cells, which demonstrated that statin-induced apoptosis can be prevented with isoprenoids supplementation but not CoQ10.[28]

Finally another explanation of statin-myopathy is the observation that statins impair intracellular calcium homeostasis by interfering with the mitochondrial respiratory chain and by affecting ryanodine receptor one (RyR1), which pumps calcium into the cytoplasm. Increased cytoplasmic calcium levels have been shown to cause cramps, myalgias and apoptosis.[29,30] Recently, genetic risk factors for statin myopathy have been identified. A strong association has been found between treatment with a high-dose statin regimen and genetic variants that affect statin blood levels, in the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial.[31] In this trial, a genome-wide analysis demonstrated that a single nucleotide polymorphism within intron 11 of SLCO1B1 on chromosome 12 was strongly associated with myopathy. The gene SLCO1B1 encodes the organic anion transporting polypeptide responsible for hepatic uptake of statins. In the SEARCH trial, the majority (60%) of myopathy cases were associated with SLCO1B1 variants.

The mechanism by which statins may induce hepatocellular injury, the other major side effect, is unclear. The depletion of mevalonate or one of its sterol metabolites caused by the inhibition of 3-hydroxyl, 3-methyl-glutaryl-CoA reductase (HMG-CoA) enzyme may be responsible for the elevated liver enzymes.[32] The type of metabolism of statins seems to be related with the hepatotoxicity of these agents. Simvastatin, lovastatin, fluvastatin and atorvastatin are indeed metabolized through cytochrome P450, while pravastatin, rosuvastatin and pitavastatin follow another metabolic pathway. Statins differ as far as lipophilicity is concerned. The less lipophilic statins, such as pravastatin, rosuvastatin, atorvastatin and fluvastatin augment the risk of aminotransferase elevation, compared to the other more lipophilic ones, although the reverse effect is observed regarding the CK elevation.[11,12] A clear explanation for this is not available even though one could implicate the hepatic organic anion transport protein (OATP or SLCO1B1) that plays an important role in facilitating the penetration of statin into the hepatocytes. It has been reported that genetic variations in SLCO1B1 have a larger effect on the area under the plasma concentration-time curve of atorvastatin than that observed with the more hydrophilic rosuvastatin.[33]

The natural history of elevated liver enzymes due to the long-term use of statins is poorly understood. However, it is recognized that in some individuals, this elevation is transient and may be physiological rather than pathological and that some patients display 'adaptation', where liver enzymes stabilize/normalize if the drug is not withdrawn.[34] There are no studies that correlate hepatic histology with elevations in liver enzymes to differentiate between true hepatotoxicity and an adaptive process. The US National Lipid Association's (NLA) Safety Assessment Task Force concluded in 2006 that there was no evidence of a relationship between elevated transaminases, statin therapy and risk of significant liver injury.[3] Furthermore, they also concluded that routine monitoring of liver enzymes did not identify those individuals at risk of developing idiosyncratic liver failure. In addition, recent evidence suggests that moderate elevation of transaminases should not contraindicate the initiation of statin therapy.

A post-hoc analysis of the secondary prevention Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study,[35] assessed the cardiovascular and liver outcomes in a total of 437 patients presenting moderately elevated liver enzymes (>3 times ULN) at enrollment, suggested that they are possibly associated with non-alcoholic fatty liver disease. Two hundred twenty seven of these individuals who were treated with a statin (mainly atorvastatin, 24 mg per day) had substantial improvement in liver tests ($p = 0.0001$), whereas the 210 individuals not treated with a statin had further increases of liver enzyme concentrations during the 3-year follow-up of this study. Furthermore, patients with abnormal liver tests who

received a statin, experienced fewer cardiovascular events in comparison to patients with abnormal liver tests who did not receive one (68% relative risk reduction, p = 0.0001). Interestingly, this cardiovascular benefit was greater (P = 0.0074) in patients with abnormal liver tests than it was in patients with normal liver enzymes.

The most frequently seen histological appearance of statin-induced liver injury is inflammation of the portal tracts with mild piecemeal necrosis and focal periportal fibrosis.[36] As serious hepatotoxicity caused by statins is rare, these findings are seldom seen. The FDA's Adverse Event Reporting System database until 2004, reported a rate of 0.69 cases of liver failure/hepatitis per million statin prescriptions, a figure similar to that reported for liver failure/hepatitis in the general adult population.[3] Analysis of an administrative database showed 6.1 to 12.8 hepatic events per 10,000 person-years of hospitalized patients on statins.[38] None were hospitalized within 6 months of starting their statin. Furthermore, only 1 of the 51741 patients who underwent liver transplantation between 1990 and 2002 was taking a marketed statin.[17,37] Adverse drug reaction reports from the UK Committee on Safety of Medicines show 4 deaths caused by atorvastatin-induced hepatotoxicity over an eight-year period (0.5 deaths per annum).[38] In addition, there are also reports of rosuvastatin, fluvastatin, and atorvastatin inducing or revealing autoimmune disease, including autoimmune hepatitis. This is an extremely rare effect and there is evidence that the hepatic effect may be reversible when the drug is withdrawn.[39-41] Finally, in very rare circumstances, statin therapy may cause liver failure.[42,43] Overall, the long-term hepatic safety of statins is reassuring. In fact, it has been reported that 24 million patient years of treatment with lovastatin reveal a rate of acute liver failure of 1 per 1.14 million patient-treatment years, which is similar to the rate of idiopathic acute liver failure.[36] Nevertheless, the potential for statin-associated severe liver injury makes the monitoring of liver enzymes during this treatment important to recognize drug-induced liver injury as early as possible.

MANAGING STATIN INTOLERANT PATIENTS

The first step is to rule out any possible conditions that increase the risk of statin-induced adverse effects. The most common of these conditions are reported in Table 1.

A complete examination should exclude related conditions such as hypothyroidism, rheumatological disorders, neuromuscular diseases, and depression. A recent study also noted that over 90% of vitamin D-deficient patients with myalgias on statins had resolution of their symptoms after 50,000 U/wk of vitamin D for 12 weeks.[44] Thus, measurements of CK, TSH, and vitamin D should be carried out if not recently done. Under routine clinical settings, a baseline CK is not necessary but is an option if the patient is at higher risk for statin-induced myopathy.[1] In asymptomatic patients, the measurement of CK is not cost effective.[45] High asymptomatic pre-treatment levels of CK should not discourage the initiation of statin treatment, provided that CK levels are <5 × ULN.[46] Recommendations to manage muscle related symptoms in patients receiving statin, have been proposed by the National Lipid Association Statin Safety Task Force 4 (Fig. 1). According with these recommendations, in patients with moderate symptoms and without significant CK elevation (<5 × ULN), progress can be followed clinically. If the muscular symptoms are severe and in those with CK elevated more than 5 × ULN, statins should be stopped. Once CK is normalized and the muscular symptoms have been resolved, patients should be rechallenged with the same or other statin at the same or lower dosage. Otherwise, different approaches can be considered (Table 2). Guidelines have also been issued to manage liver intolerance to statins (Fig. 2).[3,16,17]

An elevation of baseline hepatic transaminases <3 times ULN is not a contraindication to starting statin therapy. Non-alcoholic fatty liver disease with transaminase levels fluctuating between 1.5 and 3 × ULN is present in many patients with diabetes, metabolic syndrome, or obesity.[19] If there are no other etiologies responsible for the transaminase elevation, a low-to-moderate statin dose can be started with close monitoring alanine aminotransferase levels. The best time to recheck liver biochemistry values is not so clear. In two trials, the HPS and the AFCAPS/TexCAPS trial, the time to recheck liver profile was 3 and 2 weeks, respectively, with normalization of the values in more than 70% of the cases.[43] If the aminotransferase levels are >3 × ULN, it is recommended to stop the treatment and reassess liver tests. Although the time between the normalization of liver enzymes and the restart of medical hypolipidemic therapy is not clear, patient can continue taking the same statin and scheme or the same or another statin at lower dosage.[16,17] Conversely, when the elevation in aminotransferase levels is persistent after statin withdrawal or reoccurs after a statin rechallenge, other options should be considered. Several authors have recommended using low-dose statin treatment because of the possible greater incidence of liver enzyme elevations with higher doses. It has also been proposed that liver biochemistry monitoring should be performed every month for the first 3 to 4 months and 4 times a year thereafter. Additionally, the use of statins, which are not metabolized by the liver or the use of nonstatin compounds can be considered. A detailed evaluation of the different options to manage statin intolerant patients is reported below.

SWITCHING TO ANOTHER STATIN

Once symptoms, CK and aminotransferase levels return to baseline, a different statin with less risk for hepatotoxicity

TABLE 1. Potential risk factors for statin-induced myopathy (SIM) and hepatic side effects of statins

Statin-induced myopathy	Hepatic toxicity
Endogenous risks	Acute viral diseases
Frailty and low body mass index	Alcohol-associated liver diseases
Advanced age (>80 y)	Advanced chronic liver diseases
Multisystem disease	Mildly lipophilic statins
Renal dysfunction	Genetic factors (CYP450 isoenzymes)
Hepatic dysfunction	
Hypothyroidism	
Metabolic muscle diseases:	
Carnitine palmityl transferase II deficiency	
McArdle disease (myophosphorylase deficiency)	
Myoadenylate deaminase deficiency	
Family history of muscular symptoms	
Personal history of elevated creatinine kinase or muscular symptoms	
Genetic factors (CYP450 variants, drug transporter variants)	
Exogenous risks	
Heavy alcohol consumption	
High physical activity	
Major surgery	
Drugs affecting statin metabolism (gemfibrozil, nicotinic acid, cyclosporin, amiodarone, macrolides antibiotics, verapamil, diltiazem, systemic use of azole antifungals, warfarin, digoxin, colchicine, protease inhibitors)	
Consuming >1L of grapefruit juice per day	
Genetic factors (CYP450 variants, drug transporter variants)	

and myopathy, may be considered. The criteria to select the new statin are not well-defined. One possibility could be to change from a mildly to a highly lipophilic statin. It has been demonstrated that the less lipophilic statins (pravastatin, rosuvastatin, atorvastatin, fluvastatin) increased the relative risk of aminotransferase elevation compared to the more lipophilic ones (lovastatin, simvastatin, cerivastatin).[47] On the other hand, a change from a P450-dependent to a non-P450-dependent statin, such as fluvastatin or rosuvastatin, has been observed to decrease the risk of CK elevation. Hansen et al, in a follow-up of 45 patients with confirmed SIM, found that 43% of patients tolerated the new statin without reporting symptoms.[48]

ALTERNATE-DAY OR WEEKLY STATIN DOSING

Although this approach is a non-approved statin dosing regimen in patients with SIM, it has been based on the concept that statins with a longer half-life may maintain their hypolipidemic effect over a longer period of time. Atorvastatin has a mean terminal half-life of 14 hours and generates two active (orthohydroxy and parahydroxy) metabolites, which contribute to 70% of its HMG-CoA reductase activity and have a half-life of 20–30 hours.[49] The other statin that exhibits a half-life of 19 hours is rosuvastatin. A double-blind, placebo-controlled trial of 35 patients receiving atorvastatin, 10 mg daily versus alternate day regimen, showed LDL cholesterol reductions of

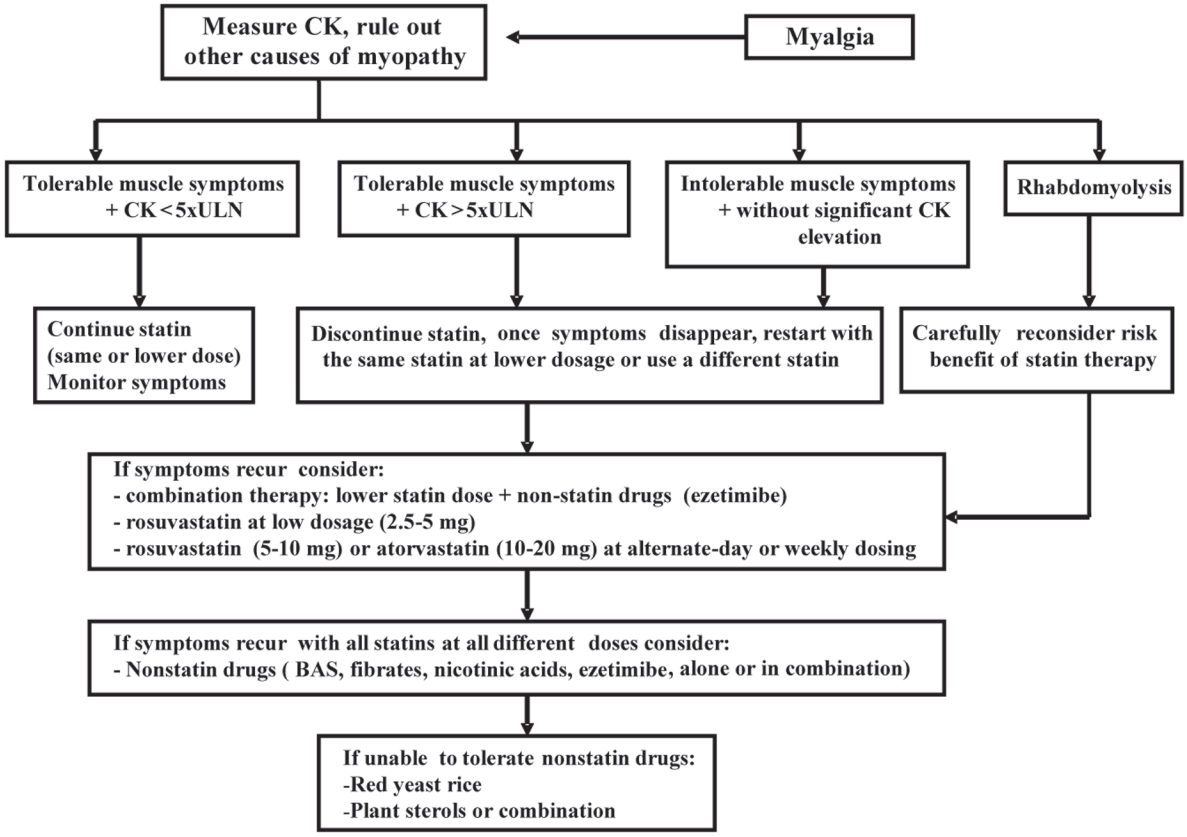

FIGURE 1. Algorithm for management of statin induced myopathy. BAS = bile acid sequestrants, CK = creatine kinase; ULN = upper limit of normal.

TABLE 2. Managing statin intolerant patients.

• Switching to another statin with different metabolism
• Selection of a statin with longer half-life and an alternate-day or weekly dosage regimen
• Combination therapy with infrequent statin dosing and ezetimibe
• Nonstatin lipid lowering drugs
• Nutraceuticals and specific diets
• LDL apheresis

38% and 35%, respectively, without any myopathy.[50] Out of 51 statin intolerant patients, who received rosuvastatin, 5 or 10 mg on alternate days, 72.5% (37 out of 51) of patients were able to tolerate this regimen without recurrence of myalgia for 4 months. Mean LDL-C decreased by 34.5% ($p<0.001$) in patients who tolerated the regimen and 50% achieved the LDL-C goal.[51]

Gadarla et al utilized rosuvastatin twice weekly (Monday and Thursday) for a time longer than 3 weeks, at doses of 5 and 10 mg, which produced a significant 26% reduction of LDL-C from baseline, in patients (mean age 62 ± 8 years) with SIM related to other lipid-lowering therapy (other statins or niacin or fibrate or combinations of these). Rosuvastatin was well tolerated by 80% of patients.[52] Once weekly rosuvastatin 5-20 mg, resulted in a mean LDL cholesterol reduction of 29% among 8 intolerant patients without any incidence of SIM. [53]

In another study with similar dosing protocol, Ruisinger et al enrolled 50 patients with a previous statin adverse event. Rosuvastatin once per week was tolerated by 37 (74%) of the 50 study participants, with doses ranging from 2.5 to 20 mg a week (mean 10 mg).[54] Patients tolerating the once-a-week regimen experienced a 17% reduction in total cholesterol, 23% reduction in LDL-C, 12% reduction in triglycerides, and a 5% increase in high density lipoprotein cholesterol (all $p=0.001$), during a mean follow-up of 4 months. The lower overall plasma concentrations from the less frequent dosing and the psychological factor of receiving only a once-weekly dose may be possible explanations for tolerance.

Although the alternate-day statin dose administration has

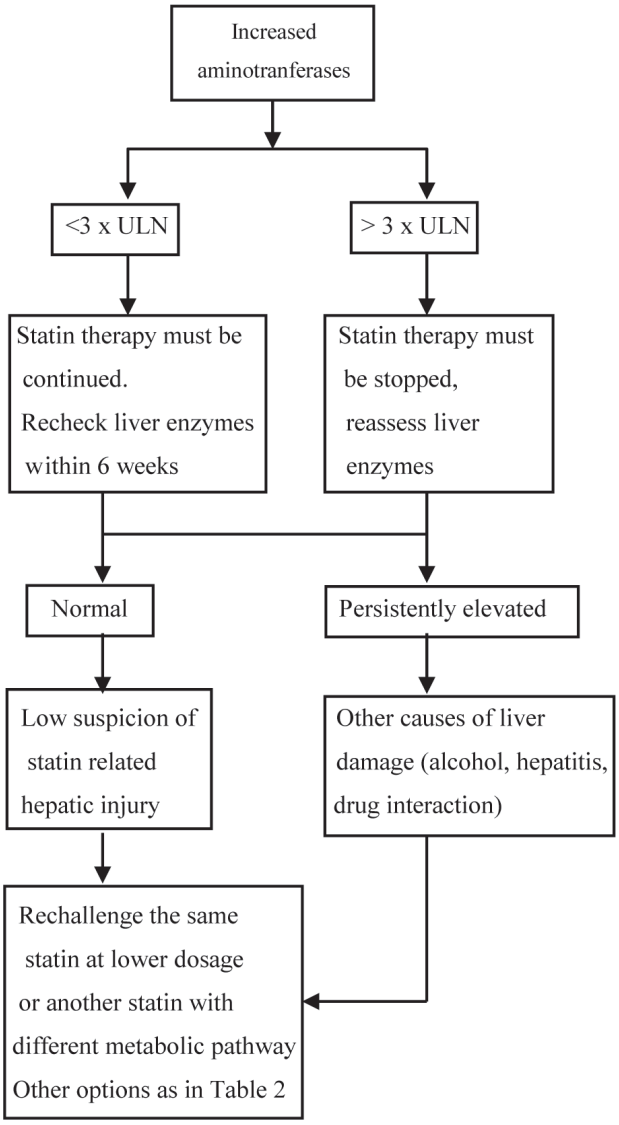

FIGURE 2. Managing the abnormal liver enzymes from statin therapy. ULN = upper limit of normal.

been demonstrated to be feasible and effective, it has some limitations. First of all, this regimen allows a lower LDL-C reduction (up to 10%–15% less) compared to the every-day regimen. This must be carefully considered in light of the ideal LDL-C target for each patient. Second, these dosing regimens have not been proven to reduce cardiovascular events. Therefore, they must be considered as an alternative treatment in well-selected patients such as those who did not tolerate more than one statin, even at lower dosage, and may otherwise go without any benefits from statin therapy. Thus, nondaily rosuvastatin and atorvastatin seem tolerable and may help lower LDL cholesterol levels in patients with statin intolerance.

COMBINATION THERAPY WITH INFREQUENT STATIN DOSING

A novel approach to managing statin intolerant patients was investigated by Athyros et al.[55] The investigators administered to 56 statin intolerant patients a combination therapy with a statin twice weekly and ezetimibe 10 mg daily. After starting ezetimibe 10 mg/day, 10 mg of atorvastatin twice weekly was added. The LDL-C was lowered by 34% and 84% of patients achieved the NCEP ATP III LDL-goal.

NONSTATIN LIPID-LOWERING DRUGS ALONE OR IN COMBINATION

Non statin lipid -lowing drugs should be considered if the patient is unable to take statins because of myopathy. These drugs may be used as monotherapy or in combination and include bile acid sequestrants (colesevelam), an intestinal cholesterol absorption inhibitor (ezetimibe), fibrates and niacin. Dosage at 3.75 g/day of colesevelam results in a 15-19% reduction of LDL-C,[56] and 10 mg at ezetimibe is able to decrease LDL-C by 15-20%.[57] In 27 statin intolerant patients the administration of ezetimibe 10 mg daily for 3 months was associated with a reduction of total cholesterol (TC) and LDL-C of 18% and 26% respectively ($p<0.001$ for both) and 25 out of 27 patients completed the three-month period without muscle pain.[58] In 66 statin-intolerant hyperlipidemic patients the administration of ezetimibe 10 mg daily for 12 weeks was associated with recurrence of muscle symptoms in 24%.[59] However, a few instances of myopathy have been reported,[60] the majority of which occurred in patients previously intolerant to statins. There are two main concerns with ezetimibe treatment. The first is that the majority of patients in ezetimibe therapy fail to achieve the LDL-C target and the second is that there are no data regarding the clinical benefit of this intervention.

Colesevelam has a favorable tolerability and drug interaction profile than cholestyramine and cholestipol. In a retrospective review Rivers et al[61] administered in 16 statin intolerant patients with diabetes mellitus and metabolic syndrome the combination of ezetimibe (10 mg/day) plus colesevelam (1.875g twice daily). The combination therapy was well tolerated and resulted in a marked reduction of both LDL-C (42.2%) and non-HDL (37.1%).

Another option for statin intolerant patients is fibrates which are effective drugs in patients with atherogenic dyslipidemia (high triglycerides and low HDL).[62] The combination of fenofibrate and ezetimibe in patients with mixed hyperlipidemia[63] reduced the LDL-C by 22%, the non-HDL-C by 31.6% and the apoB by 25.2%; additionally the above mentioned combination increased the HDL-C by 20.9% and with this

combination the incidence of muscle symptoms was very low.

Another possible alternative in statin intolerant-patients is niacin alone or associated with laropiprant. Niacin has been reported to be effective in reducing LDL-C, triglycerides and increasing HDL.[64,65] At present no data are available in the literature on the use of nicotinic acid in statin-intolerant patients.

LDL APHERESIS

This type of LDL-C lowering treatment can be applied in coronary patients intolerant to statins (or any other lipid lowering drug) whose LDL-C levels remain >5 mmol/L (193 mg/dL) despite maximum non-statin lipid-lowering medication.[66]

DIETARY MANIPULATION AND LIPID LOWERING NUTRACEUTICALS

For dyslipidemic patients who cannot tolerate statins, a reasonable approach is a more intensive lipid-lowering dietay intervention. This may be obtained by combining dietary ingredients with cholesterol-lowering properties, like 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). Jenkins et al evaluated the efficacy of this intensive diet versus lovastatin in 46 hyperlipemic adults, who were randomly assigned to a diet very low in saturated fat (control); the same diet plus lovastatin 20 mg/d (statin); or a diet high in plant sterols (1.0 g/1000 kcal), soy protein(21.4 g/1000 kcal), viscous fibers (9.8 g/1000 kcal), and almonds (14 g/1000 kcal) (dietary portfolio).[67] After four weeks, changes in LDL-C were 8.0% ($p = 0.002$), 30.9% ($p = 0.001$), and 28.6% ($p = 0.001$), in the control, statin and diets, respectively. It is important to note that this intensive diet led to a cholesterol reduction that was comparable to that observed with statin. Limitation of this intensive diet is the palatability, because only 40% of participants found this diet acceptable.

An alternative option may be the dietary supplementation with nutraceuticals. Among these compounds, the yeast rice is of particular interest. 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.[68]

Becker et al randomly assigned 62 statin-intolerant dyslipidemic patients (baseline LDL-C 163.3 mg/day) to receive red yeast rice 1800 mg twice daily or placebo for 24 weeks and reported a 22% differential decrease in LDL at 12 weeks and 12% at 24 weeks.[69] Only 2 of the 31 (6.5%) patients on red yeast rice could not tolerate this regimen, due to myalgias.

In another study which compared red yeast rice vs pravastatin, 20 (95%) out of 21 statin- intolerant patients were able to tolerate without myalgias 2400 mg twice daily, with a 30% LDL-C lowering vs 27% in pravastatin group (20 x 2 daily) after 12 weeks of treatment.[70] A more recent retrospective study[71] reported that most (92%) of 25 statin –intolerant patients, who underwent treatment with red yeast rice tolerated the nutraceutical at a dose of 1200 mg at bed time for more than 4 weeks, achieving a 21% LDL-C reduction.

Different commercial preparations of red yeast rice (RYR) have different concentrations of monacolins, the bioactive ingredients[69] and the long-term safety of the regular consumption of these products is not fully documented. For this reason the EAS recommend the utilization of the red yeast rice supplement with a level of evidence B.[72]

IS THERE ANY ROLE FOR SPECIFIC TREATMENTS TO ATTENUATE STATIN INTOLERANCE?

It has been reported that SIM may be due to the statin induced reduction of CoQ10. Supplementation of CoQ10 increases its blood levels, but it is unclear whether this has a favorable effect on statin induced myopathy.[73] In a successful trial with CoQ10 supplementation, in patients with myopathic symptoms,[74] pain severity decreased by 40% ($p<0.001$) and pain interference with daily activities decreased by 38% ($P<0.02$) in patients who treated with CoQ10. However, these findings have not been replicated in larger trials. Therefore, the routine use of CoQ10 is not recommended in statin-intolerant patients.

Vitamin deficiency is associated with myalgias and poor muscle function.[75] This knowledge has led to the exploration of the potential benefits of vitamin supplementation in SIM. In a recent but small trial with statin-intolerant patients and vitamin D levels below 32 mg/ml, the administration of vitamin D supplementations for 3 months increased vitamin D levels and 92% of patients were free of myalgias.[76] These results, although interesting, need to be validated by a large double blind placebo-controlled trial. Today there is no specific recommendation for the alleviation of symptoms related to statin induced myopathy..

CONCLUSION

Intolerance to statins is frequently faced in clinical practice. This is mostly due to muscular symptoms and/or elevation of hepatic aminotransferases, which overall constitute approximately two-thirds of reported adverse events during statin therapy. The first step in handling statin-intolerant patients is to rule out any secondary causes of myopathy or liver toxicity. The second step is to determine whether the adverse effects are indeed related to statin therapy by statin dechallenge and

rechallenge. Another option is to restart with the same statin at a lower dosage or to switch to another statin with different pathways of metabolism. If the symptoms are recurrent, different approaches should be considered, such as unconventional dosing (every-other-day or weekly administration) of statins with longer half-life. Another option in patients who cannot tolerate statins is the use of nonstatin lipid-lowering drugs (ezetimibe, bile acids sequestrants and fibrates) alone or in combination. Concerning low-risk individuals, the use of herbal supplements effective in reducing LDL-C can be considered. However, the need for randomized trials which directly compare lipid-lowering agents, and assess more properly the incidence of milder myopathies is mandatory.

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