Considerations for Safe Use of Statins: Liver Enzyme Abnormalities and Muscle Toxicity

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Statins play an important role in the care of patients with cardiovascular disease and have a good safety record in clinical practice. The risk of hepatic injury caused by statins is estimated to be about 1 percent, similar to that of patients taking a placebo. Patients with transaminase levels no more than three times the upper limit of normal can continue taking statins; often the elevations will resolve spontaneously. Coexisting elevations of transaminase levels from nonalcoholic fatty liver disease and stable hepatitis B and C viral infections are not contraindications to statin use. Although myalgias are common with statin use, myositis and rhabdomyolysis are rare. When prescribed at one-half the recommended maximal dosage or less, statins are associated with an incidence of myopathy similar to that of placebo; therefore, routine monitoring of creatine kinase levels in asymptomatic patients is not recommended. Myopathic symptoms usually resolve approximately two months after discontinuing the statin, and the same statin can be restarted at a lower dosage, or patients can try a different statin. Clinically important drugs that interact with statins and increase the risk of adverse effects include fibrates, diltiazem, verapamil, and amiodarone. (*Am Fam Physician.* **2011;83(6):711-716. Copyright © 2011 American Academy of Family Physicians.)**

The incidence of true liver injury caused by statin therapy is low (about 1 percent). The dose-related elevations of alanine transaminase and aspartate transaminase levels observed in patients taking statins do not exceed those in patients taking placebo at low to moderate dosages (one-half the maximal dosage or less) and are modest at higher dosages. Many preexisting conditions that cause elevations in transaminase levels (e.g., chronic viral hepatitis, nonalcoholic fatty liver disease) were once thought to be contraindications to statin therapy; however, statins do not worsen liver function in most patients with chronic liver disease.[1-7]

Statins and the Liver

Elevations in transaminase levels do not reflect hepatic injury per se; the best indicator of true liver injury is the serum bilirubin level.[1] Meta-analyses of randomized placebo-controlled trials demonstrate that low to moderate dosages of statins are not associated with clinically significant (i.e., greater than three times the upper limit of normal) elevations in transaminase levels.[2,8] Maximal recommended dosages of lovastatin (Mevacor),[9] pravastatin (Pravachol),[10] simvastatin (Zocor),[11] atorvastatin (Lipitor),[8] and rosuvastatin (Crestor)[8] were associated with modest but notable increases in transaminase levels. Many of these elevations will resolve with continued therapy.[1]

NONALCOHOLIC FATTY LIVER DISEASE

The presence of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis should not deter physicians from using statins in patients with hyperlipidemia. Some studies even suggest that statins may have a beneficial effect on underlying liver disease.[12]

Two retrospective studies examining 7,473 patients with mildly elevated transaminase levels found fewer severe increases in transaminase levels in patients using statins than in patients not using them over a 12-month period.[3,4] In another matched study of 2,264 patients, those taking statins showed no differences in liver enzyme levels or progression of steatohepatitis compared with patients not taking statins.[13] A small study of

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Elevated transaminase levels and nonalcoholic fatty liver disease are not contraindications to statin use.	C	1-4	Expert opinion,[1] meta-analysis,[2] small case-control studies[3,4]
Stable hepatitis C infection is not an absolute contraindication to statin use.	C	5-7	Small cohort study[5]; small prospective, double-blind, placebo-controlled study[6]; large cohort study[7]
Statin-induced myopathy is dose-related and may occur with all statins.	C	17	Systematic review of observational studies
Baseline levels of creatine kinase need to be obtained only in patients at high risk of muscle toxicity.	C	1, 16	Consensus guidelines

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

68 patients with biopsy-proven nonalcoholic fatty liver disease showed no change in liver enzymes but a statistically significant 46 percent reduction in the quantitative steatosis on repeat biopsy in the 17 patients taking statins at follow-up.[14] Two small studies evaluating patients with nonalcoholic steatohepatitis showed no change (seven patients)[15] or a reduction (five patients)[12] in liver enzymes among those taking statins; both studies also demonstrated some degree of improvement in liver pathology.

CHRONIC VIRAL HEPATITIS

Evidence suggests that patients with chronic hepatitis B and C infections may safely use statins, although supporting data are not as strong as those for patients with nonalcoholic fatty liver disease. A retrospective cohort study of 13,492 patients taking lovastatin[5] and a prospective study of 320 patients taking pravastatin[6] found no evidence of increased hepatotoxicity among those with chronic liver disease (including hepatitis B and C infections). A cohort study showed that patients with hepatitis C infection who took statins had less severe elevations in transaminase levels than patients with hepatitis C infection who were not on statins or those who took statins but tested negative for hepatitis C infection.[7]

An expert consensus panel of hepatologists convened by the National Lipid Association concluded that chronic liver disease is not a contraindication to statin use. Although the panel also concluded that routine monitoring of liver function was not supported by the literature, for medicolegal reasons they recommended checking transaminase levels before initiating therapy, 12 weeks after initiating therapy or increasing the dosage, and periodically thereafter.[1]

Statins and Muscle

Myopathy is a general term describing any disease of the muscles. Myalgia is defined as muscle ache or weakness without elevated creatine kinase (CK) levels, whereas myositis denotes muscle symptoms with elevated CK levels. Rhabdomyolysis indicates muscle symptoms with a CK elevation greater than 10 times the upper limit of normal associated with creatinine elevation (usually with brown urine and urinary myoglobin).[16] Myalgias are common with statin use. However, myositis and rhabdomyolysis are far less common, with rates of 5.0 and 1.6 per 100,000 patient-years, respectively; these rates appear to be similar with all statins, although well-designed comparative studies are lacking.[17] The mechanism of statin-induced muscle injury is uncertain.[18]

RISK FACTORS FOR MUSCLE TOXICITY

Several factors may increase the likelihood of statin-induced myopathy *(Table 1)*.[16] Multiple clinical trials have found that the risk of myopathy is dose-dependent, especially with simvastatin.[17,19] The U.S. Food and Drug Administration recently cautioned about the increased risk of muscle injury from the 80-mg dose of simvastatin.[20] A systematic review of placebo-controlled trials found that the incidence of statin-related myopathy from low to moderate dosages (40 mg per day or less) is similar to that with placebo (approximately 5 percent).[17] High dosages (more than 40 mg per day) are associated with myopathic symptoms in 5 to 18 percent of patients.[19]

Myopathy risk increases when statins are taken with medications known to inhibit their metabolism *(Table 2)*.[11,17,18,21-32] Serum levels of simvastatin and lovastatin are increased four- to sixfold in conjunction with erythromycin and verapamil therapy, and 10- to 20-fold with itraconazole (Sporanox) and cyclosporine (Sandimmune) therapy.[11,21,22,25,27] Simvastatin and lovastatin levels are increased threefold and rosuvastatin levels are increased twofold in patients also taking gemfibrozil (Lopid).[11,22,28] The rate of rhabdomyolysis was 0.44 per 10,000 patient-years with statin monotherapy versus 5.98 when the statin was combined with a fibrate. This interaction appears to be more notable with gemfibrozil than fenofibrate (Tricor).[32]

Patients who have disease states or are taking concomitant medications known to independently cause myalgias are more likely to experience muscle injury when statin therapy is initiated. Untreated hypothyroidism[33] and alcohol abuse[34] may predispose patients to myopathic symptoms from statin therapy. Gemfibrozil and niacin, often used in patients taking statins, have their own associated risks of myopathy,[32] although these appear to be rare and have not been confirmed by large, well-designed studies.[18,35] Evidence does not support the hypothesis that lipophilic statins (e.g., lovastatin, simvastatin, atorvastatin), which penetrate muscle fibers more easily, are more likely to cause muscle toxicity than hydrophilic statins (e.g., pravastatin, rosuvastatin).[18]

Table 1. Risk Factors for Statin-Induced Myopathy

Factors associated with increasing statin plasma concentration
Age older than 70 years
Drug-drug interactions
Female sex
High-dose therapy (greater than one-half the maximal recommended dosage)
Impaired liver/renal function (creatinine clearance < 30 mL per minute per 1.73 m^2 [0.50 mL per second per m^2])
Low body mass
Untreated hypothyroidism
Factors predisposing muscle to injury
Additive drug adverse effects
Alcohol abuse
Substance abuse (e.g., cocaine, amphetamines, heroin)
Untreated hypothyroidism

Information from reference 16.

PREVENTION OF STATIN-INDUCED MUSCLE INJURY

Strategies to reduce the risk of statin-induced myopathy include using the lowest effective dosage, identifying patient risk factors, monitoring adverse effects and CK levels in symptomatic patients, avoiding serious drug interactions, and educating patients. Although the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommends measuring baseline CK levels in all patients, other experts recommend obtaining baseline CK levels only in patients at high risk of muscle toxicity.[1,16,18,36] Asymptomatic patients do not require routine measurement of CK levels. *Figure 1* provides an algorithm for the evaluation and treatment of patients with myopathic symptoms.[37] These usually resolve approximately two months after discontinuing statin

Table 2. Summary of the Major Interactions with Statins

Nonstatin drug/substance	*Statins affected*	*Recommendation*
CYP3A4 inhibitors		
Azole antifungals	Atorvastatin (Lipitor)	Avoid lovastatin and simvastatin[11,21,22]
Itraconazole (Sporanox)	Lovastatin (Mevacor)	Use caution when exceeding 20 mg per day of atorvastatin[23]
Ketoconazole	Simvastatin (Zocor)	
Calcium channel blockers		
Diltiazem (Cardizem)		Do not exceed 20 mg per day of lovastatin or 10 mg per day of simvastatin[11,17,18,22,24]
Verapamil		Do not exceed 40 mg per day of lovastatin or 20 mg per day of simvastatin[11,17,18,22,24,25]
Other		
Grapefruit juice (more than 1 quart per day)		Avoid atorvastatin, lovastatin, and simvastatin[11,22,26]
CYP3A4/organic anion transporting polypeptide inhibitors		
Cyclosporine (Sandimmune)	All statins	Do not exceed 10 mg per day of atorvastatin, 20 mg per day of lovastatin, or 5 mg per day of rosuvastatin (Crestor)[22,27,28]
		Use caution with fluvastatin (Lescol)[29]
		Avoid pitavastatin (Livalo)[30] and pravastatin (Pravachol)[27]
Macrolide antibiotics	Atorvastatin	Avoid lovastatin and simvastatin[11,17,18,22,24,25]
Clarithromycin (Biaxin)	Lovastatin	Do not exceed 1 mg per day of pitavastatin[30]
Erythromycin	Pitavastatin	Use caution when exceeding 20 mg per day of atorvastatin[17,23,27,31]
	Simvastatin	
Protease inhibitors	All statins	Avoid lovastatin, pitavastatin, and simvastatin[11,17,18,22,24]
Atazanavir (Reyataz)		
Ritonavir (Norvir)		Do not exceed 20 mg per day of atorvastatin or 10 mg per day of rosuvastatin[11,23,28]
Lopinavir/ritonavir (Kaletra)		
CYP3A4/CYP2C9 inhibitor		
Amiodarone (Cordarone)	Atorvastatin	Consider limiting atorvastatin dose[17,18,23,24]
	Fluvastatin	Do not exceed 40 mg per day of lovastatin or 20 mg per day of simvastatin[11,17,22,24]
	Lovastatin	
	Simvastatin	Use caution with fluvastatin[29]
CYP2C9, CYP2C19, glucuronidation, and organic anion transporting polypeptide inhibitors		
Gemfibrozil (Lopid)	All statins	Avoid pravastatin unless benefits outweigh risks[32]
		Consider limiting atorvastatin dose
		Do not exceed 10 mg per day of rosuvastatin or simvastatin[11,28,32]
		Do not exceed 20 mg per day of lovastatin[22]
		Use caution with fluvastatin[29] and pitavastatin[30]
CYP2C9 inhibitor		
Fluconazole (Diflucan)	Fluvastatin	Use caution[29]

CYP = cytochrome P450.

Information from references 11, 17, 18, and 21 through 32.

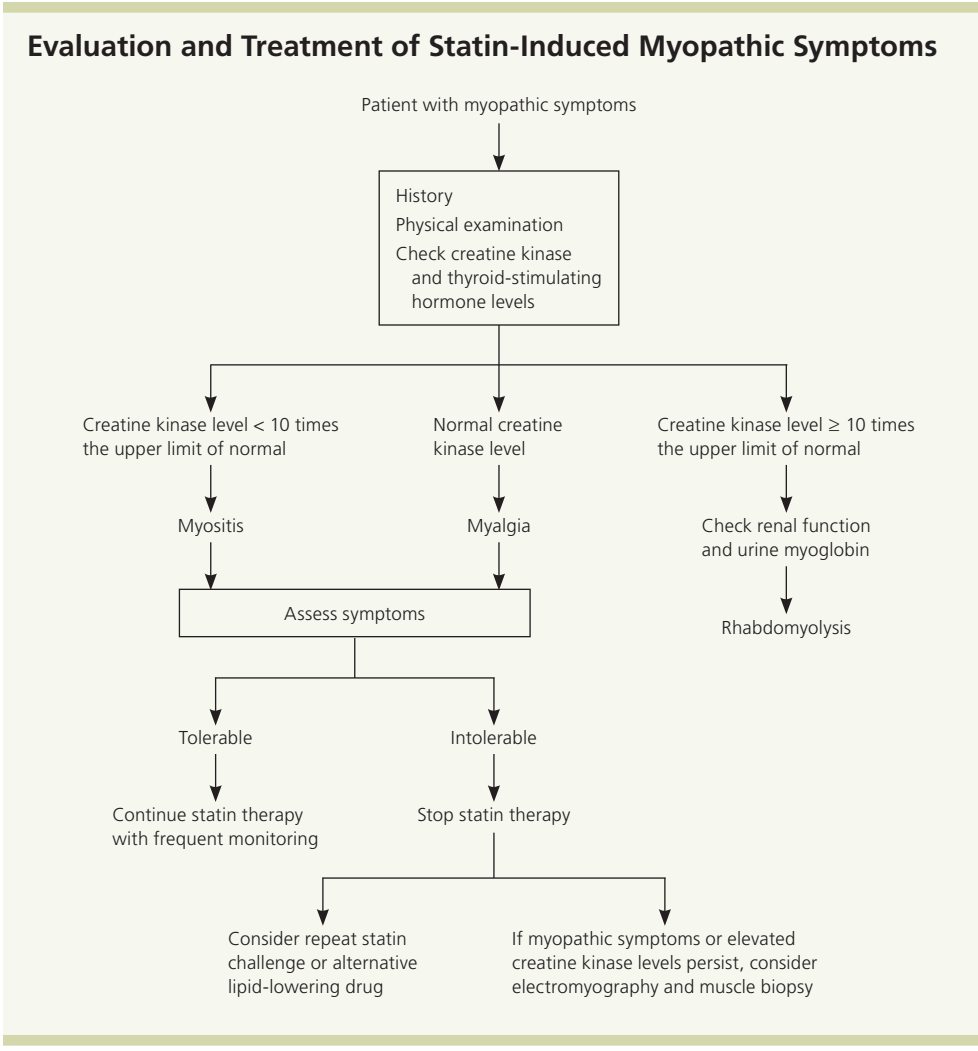

Figure 1. Algorithm for the evaluation and treatment of patients with statin-induced myopathic symptoms.

Adapted with permission from Sathasivam S, Lecky B. Statin induced myopathy. BMJ. *2008;337:a2286.*

therapy; patients can then restart the statin at a lower dosage or try a different statin. In a retrospective cohort study, 43 percent of patients remained asymptomatic on statin rechallenge, with 32 percent of patients tolerating a different statin and 11 percent tolerating a lower dosage of the same statin.[38]

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