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Safety of statins: Effects on muscle and the liver

ABSTRACT

Although statin drugs can have adverse effects on muscles and the liver, these effects are uncommon. Caution is warranted in patients at higher risk, ie, those who are elderly, frail, or small; have multisystem disease; are receiving immunosuppressive drugs or other medications that interact with statins; or are receiving higher doses of a statin.

KEY POINTS

Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be measured in all patients before starting a statin. However, elevations of up to three times the upper limit of normal do not pose contraindications to statin therapy.

ALT and AST should be monitored periodically during statin therapy. New elevations should be evaluated, as should new muscle symptoms.

Whether creatine kinase should be measured at baseline and monitored during statin therapy is not known, but many experts recommend it.

The use of statins in patients with nonalcoholic fatty liver disease appears effective and safe.

Recommendations regarding the use of statins are available from an advisory committee of the American College of Cardiology, American Heart Association, and National Heart, Lung, and Blood Institute (*Stroke* 2002; 33:2337–2341).

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THE TWO MOST clinically important adverse effects of statins are hepatotoxicity, reflected by increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and myopathy, which includes a range of muscle symptoms and elevated serum markers of muscle injury such as creatine kinase (CK), AST, and aldolase.

These two side effects are worrisome for both physicians and patients, as they have a bearing on long-term adherence and compliance with drug use.

This review addresses the incidence of these adverse effects, the risk-benefit ratio of statins, possible causative mechanisms, and how to clinically manage the mild presentations of these effects so that physicians may feel more comfortable prescribing these life-saving medications.

STATINS ARE BENEFICIAL

The first statin was approved for treating hypercholesterolemia in 1987, and the statins are now one of the most widely prescribed classes of medications.

In clinical trials, five of the six approved statins have shown evidence of reducing coronary heart disease events in a wide range of patient populations, both with and without baseline cardiovascular disease. Furthermore, experimental and clinical evidence suggests that statins directly reduce inflammation, improve endothelial function, and stabilize atherosclerotic plaque independently of their lipid-lowering effects. The clinical benefits of statin therapy appear to be overwhelmingly favorable in patients whose short-term risk of coronary heart disease is high, ie, more than 2% per year.

TABLE 1

Statin drugs at a glance

DRUG	TABLET SIZES (MG)	BIOAVAILABILITY (%)	METABOLISM	HALF-LIFE (HOURS)	% REDUCTION IN LIPIDS*			
					TC	LDL-C	HDL-C	TG
Atorvastatin (Lipitor)	10, 20, 40, 80	14	CYP3A4	14	25–45	26–55	5–13	17–53
Fluvastatin (Lescol)	20, 40, 80	24	CYP2C9	0.5–3	16–27	22–36	3–11	12–25
Lovastatin (Mevacor)	10, 20, 40	< 5	CYP3A4	2–4	16–34	21–42	2–10	6–27
Pravastatin* (Pravachol)	10, 20, 40, 80	17	Sulfation	2–3	16–25	22–34	2–12	15–24
Rosuvastatin* (Crestor)	5, 10, 20, 40	20	CYP2C9	19	33–46	45–58	8–14	10–35
Simvastatin (Zocor)	5, 10, 20, 40, 80	5	CYP3A4	1–3	19–36	26–47	8–16	12–34

*TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, TG = triglycerides

However, this benefit must be balanced with the risks of statin therapy, since patients must take these agents for many years, if not indefinitely.

HOW STATINS WORK

Hydroxymethylglutaryl-coenzyme A reductase (HMG-CoA reductase) is the rate-limiting enzyme for cholesterol synthesis in the liver and other tissues. By competitively inhibiting hepatic HMG-CoA reductase, statins reduce hepatocyte cholesterol content and stimulate expression of receptors for low-density lipoprotein cholesterol (LDL-C), which enhances removal of LDL-C from the circulation. These drugs have become the preferred pharmacologic method of reducing LDL-C levels.

X-ray crystallographic studies[1] have determined the structure of the catalytic portion of HMG-CoA reductase that forms complexes with statins. These studies show that the HMG-like structural moiety common to all statins occupies the HMG-binding site of the reductase enzyme, thus sterically inhibiting the conversion of HMG-CoA to mevalonate.

The key pharmacologic, pharmacokinetic, and efficacy data of the currently available statins are listed in TABLE 1. As a class, the statins are well tolerated and rarely have severe adverse effects. Common adverse effects include gastrointestinal disturbances, dyspepsia, headache, myalgia, central nervous system disturbances, and sleep disorders.[2,3]

EFFECTS OF STATINS ON MUSCLE

The risk of rhabdomyolysis may in part be genetically determined

The seriousness of the effect of statins on muscle was highlighted by the voluntary withdrawal of cerivastatin (Baycol) in 2001 due to cases of fatal rhabdomyolysis. This effect appeared to occur most often with higher doses, in the elderly (particularly women), and when cerivastatin was used in combination with gemfibrozil. This experience has helped to shape our clinical opinion about the potential muscle risk with the other statins.

The first description of muscle adverse events related to lipid-altering drugs was with clofibrate and was published more than 35 years ago. Since then, myopathies have been reported with several lipid-lowering drugs, used either alone or in combination.[4–6]

In reports of clinical trials of statins, the term "myopathy" has been used loosely to designate muscle symptoms such as pain with or without CK elevation or weakness. A clinical advisory on statins from the American College of Cardiology (ACC), American

Heart Association (AHA), and National Heart, Lung, and Blood Institute (NHLBI)[7] gave the following definitions:

- Myopathy—a general term for any disease of muscle
- Myalgia—muscle aches or weakness without CK elevation
- Myositis—muscle symptoms with CK elevation.

Incidence of myopathy is low

In controlled clinical trials, the incidence of statin-related myopathy is low—0.1% to 0.2% over periods of time from 8 weeks up to 52 weeks.[8]

Pooled data from 44 clinical trials[9] involving 16,495 dyslipidemic patients treated with atorvastatin 10 to 80 mg (n = 9,416), placebo (n = 1,789), or other statins (n = 5,290) revealed persistent elevation in CK of more than 10 times the upper limit of normal in only one atorvastatin-treated patient, who had no clinical symptoms. The incidence of treatment-associated myalgia was also low (1.9% with atorvastatin, n = 181; 0.8% with placebo, n = 14; 2.0% with other statins, n = 105), and was not related to the dose.

Reported incidence of fatal statin-induced rhabdomyolysis: < 1 per million

In a recent review of rosuvastatin safety,[10] with a database of 12,400 patients receiving 5 to 40 mg, the incidence of CK concentrations greater than 10 times the upper limit of normal was 0.4%, and no cases of rhabdomyolysis were reported. The incidence of myalgia, irrespective of cause, was 3.1%.

In the Heart Protection Study,[11] after a run-in phase of 4 to 6 weeks, 10,269 patients were randomized to receive either simvastatin 40 mg/day or placebo. During the 5 years of the trial, CK concentrations rose to 4 to 10 times the upper limit of normal in 0.2% of the simvastatin group vs 0.13% of the placebo group, while CK concentrations greater than 10 times the upper limit of normal occurred in 0.11% of simvastatin recipients vs 0.06% of placebo recipients. Rhabdomyolysis occurred in 0.05% of simvastatin-treated patients compared with 0.03% of placebo recipients. Of note, there was no significant difference in the number of participants whose medication was discontinued because of muscle symptoms.

These data confirm the very low incidence of elevated CK levels, with or without symptoms.

Rhabdomyolysis is the most serious presentation

Rhabdomyolysis, the most serious presentation of myopathy, involves severe skeletal muscle injury and cell death.[12] Potential initiating causes include trauma, infection, toxins, genetic abnormalities, and drugs such as statins. Several mechanisms have been proposed to explain how statins in myocytes may alter cellular function and result in myocyte death. A detailed discussion of this topic is beyond the scope of this article and can be found elsewhere.[13,14]

As the muscle cells break down, they release myoglobin, a variety of enzymes (eg, CK, AST, and aldolase), potassium, creatinine, and other intracellular constituents into the circulation, potentially leading to irreversible renal failure, cardiac arrhythmias, and local compartment syndromes due to intracellular fluid shifts.

Marked CK elevations (> 10 times the upper limit of normal), myoglobinuria (urine dipstick-positive for blood without red cells), and renal insufficiency are frequently used as criteria for the clinical diagnosis of rhabdomyolysis. A clinical sign is dark brown urine due to myoglobinuria.

As of June 2001, cases of fatal rhabdomyolysis had been reported to the Adverse Event Reporting System of the US Food and Drug Administration at a rate of less than 1 death per million prescriptions for all statins, except for cerivastatin, which had an incidence of more than 3 deaths per million prescriptions.[15]

Factors promoting statin myopathy

Genetics. The risk of rhabdomyolysis may in part be genetically determined. Up to one fourth of patients with recurrent rhabdomyolysis may have an underlying genetic predisposition,[16] such as an abnormality in a muscle enzyme such as phosphorylase, phosphofructokinase, carnitine palmitoyl transferase, or myoadenalate deaminase. The diagnosis of these abnormalities is complex and involves biopsy evidence of muscle pathology and assaying muscle activity.

Statin pharmacodynamics. The mechanism of statin myopathy is unclear, but appears to be related to serum levels of the active molecules that inhibit HMG-CoA reductase. In addition, the ability of the drugs to cross cell membranes, a function of lipophilicity, may influence how much cholesterol synthesis inhibitory activity occurs.

Bioavailability is probably not a major factor for the currently available statins, since they all have relatively low bioavailability (< 20%). In contrast, cerivastatin had a much higher bioavailability (60%).

Drug interactions. Lovastatin, simvastatin, and atorvastatin are metabolized mainly by cytochrome P450 CYP3A4.[17] Inhibition of CYP3A4 can increase serum levels of these statins, and there have been several case reports of myopathy, including rhabdomyolysis, when these drugs were given with drugs that competitively inhibit CYP3A4 (TABLE 2).

Pravastatin does not undergo metabolism through the CYP450 system; it is metabolized by sulfation and conjugation.

Fluvastatin is metabolized mainly by CYP2C9 and to a lesser extent by CYP3A4 and CYP2D6. Although there have been reports of myopathy with pravastatin and fluvastatin, the reporting rate for coadministration with CYP3A4 inhibitor drugs is rare.

Rosuvastatin is metabolized mainly by CYP2C9 and CYP2C19; however, case reports of myopathy that occurred with rosuvastatin are most likely related to the use of doses higher than those clinically indicated (ie, 80 mg).

Drugs that affect statin metabolism through pathways other than CYP450 are cyclosporine and gemfibrozil. Cyclosporine significantly increases the maximum concentration of all statins, and recent data suggest that gemfibrozil competitively inhibits statin glucuronidation, thereby also increasing the maximum concentration of all statins.

Combination of factors. Therefore, risk of myopathy with statins is most likely a combination of genetic predisposition, effects of older age on drug metabolism, and altered statin metabolism due to drug interactions that results in higher-than-expected plasma levels of active statin compounds.

For the clinician, the important point to remember concerning statin-induced muscle effects is that the mechanism is not known but is probably related to high statin plasma levels, which can result from drug interactions (especially with CYP3A4 inhibitors, cyclosporin, and gemfibrozil) or use of maximum approved statin doses. Increased age, particularly in women, and possibly genetic predisposition are also important determinants of myopathy risk.

TABLE 2

Factors that increase risk of statin-associated myopathy

- Age > 70 (women at higher risk than men)
- Frailty and small body frame
- Multisystem disease (eg, chronic renal insufficiency, heart failure)
- Solid organ transplant recipients
- Polypharmacy
- Perioperative period
- Specific concomitant medications
  - Fibrates (especially gemfibrozil)
  - Nicotinic acid (rarely)
  - Cyclosporine
  - Azole antifungals (itraconazole and ketoconazole)
  - Macrolide antibiotics (erythromycin and clarithromycin)
  - Protease inhibitors (for human immunodeficiency virus infection)
  - Nefazodone
  - Verapamil
  - Amiodarone
  - Large quantities of grapefruit juice (usually more than 1 quart per day)
  - Alcohol abuse

ADAPTED FROM DATA FROM PASTERNAK RC, SMITH SC JR, BAIREY-MERZ CN, GRUNDY SM, CLEEMAN JI, LENFANT C. ACC/AHA/NHLBI CLINICAL ADVISORY ON THE USE AND SAFETY OF STATINS. STROKE 2002; 33:2337–2341.

STATINS AND LIVER EFFECTS TO WATCH FOR

Since statins inhibit cholesterol synthesis in the liver much more than in any other tissue,[18] it is not surprising that elevations in the liver enzymes ALT and AST have been noted since the first clinical trials with lovastatin.

There are four hepatic syndromes to be considered in the context of statin therapy: acute liver failure, hepatitis, cholestasis, and "transaminitis" (asymptomatic elevation of ALT and AST levels).

Acute liver failure

The most serious hepatic adverse effect is acute liver failure. The incidence of acute liver failure in the general population is about 1:130,000, and the projected incidence of statin-induced acute liver failure is nearly the same, at 1:114,000.[19] There is no evidence that minor asymptomatic elevations of ALT and AST precede acute liver failure, nor is there support for routine screening or monitoring for acute liver failure.[20]

Perger et al[21] reviewed reports of the Adverse Event Reporting System of the World Health Organization for deaths resulting from serious liver injury that could be attributed to statin therapy. The calculated rates per million prescriptions were as follows:

- Atorvastatin 0.07 (95% confidence interval 0.03–0.14)
- Fluvastatin 0.05 (0.006–0.20)
- Simvastatin 0.02 (0.0002–0.05)
- Pravastatin 0.04 (0.007–0.11)
- Lovastatin 0.04 (0.006–0.09).

The median age of patients developing severe liver toxicity for all statins was 64 years (range 21–88), and both sexes were equally affected.

Cyclosporine and gemfibrozil increase the concentration of all statins

Hepatitis, cholestasis are rare

The major statin trials have not reported any cases of cholestasis or severe hepatitis, suggesting that these are rare.[20]

Transaminitis: Same incidence with statins vs placebo

During postmarketing surveillance, clinically significant elevations in AST and ALT (more than three times the upper limit of normal) have been reported in 1% of patients. These elevations were dose-related and comparable among the various statins, although not always significantly increased compared with placebo.[22] Most elevations occur within the first 3 to 6 months of therapy and reverse when the statin is stopped, so that monitoring for this adverse effect is helpful during this period.

A meta-analysis of the three major randomized clinical trials of pravastatin—the Cholesterol and Recurrent Events (CARE) trial, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, and the West of Scotland Coronary Prevention Study (WOSCOPS)—assessed safety data from more than 112,000 person-years of exposure[23] and found no differences in serious noncardiovascular adverse events between the groups receiving pravastatin and placebo. In particular, the percentage of patients with ALT levels three times the upper limit of normal or higher was 1.4% with both pravastatin and placebo.

In the Heart Protection Study, ALT levels increased to two to four times the upper limit of normal in 1.4% of simvastatin recipients and 1.3% of placebo recipients. Levels rose to more than four times the upper limit of normal in 0.4% of simvastatin recipients and 0.3% of placebo recipients. Furthermore, there was no difference between the treatment and placebo groups in the number of patients whose study medication was discontinued because of elevated ALT (0.05% with simvastatin vs 0.03% with placebo).

As previously mentioned in the controlled clinical trials of rosuvastatin, the incidence of clinically significant ALT increases was low and similar across all doses: 0.5% at 5 mg (among 1,317 patients), 0.1% at 10 mg (among 7,726 patients), 0.1% at 20 mg (among 3,882 patients), and 0.3% at 40 mg (among 3,957 patients). In most cases, the increases were transient and resolved or improved with continued treatment, with or without downward dose titration. In addition, clinically significant ALT increases occurred in the same proportion (0.2%) as in other statin comparator groups, which included 10 to 40 mg of pravastatin (n = 1,260).

Smith et al[24] reviewed the computerized medical records of a primary care practice and identified all patients receiving a statin who had ALT, AST, and CK values documented during 1998. During 1998, 1,014 (85%) of the 1,194 patients who had a statin on their medication list had at least one of the monitoring tests performed. Of these, 10 (1.0%) had a significant elevation in AST or ALT (more than three times the upper limit of normal) and 5 (0.5%) a moderate elevation (two to three times the upper limit of normal), but none of these abnormalities appeared to be related to statin use. There were no documented adverse sequelae associated with the abnormal aminotransferase levels.

This study not only confirmed the very low incidence of elevated aminotransferases with statins, it questioned the usefulness of routine measurement of them in all patients taking statins.

A similar conclusion was reached in a recent evaluation of a large health maintenance organization database for causes of severe statin-related transaminitis.[25]

If AST and ALT are elevated at baseline

The most important clinical question is what to do with patients who are definite candidates for statin therapy but have baseline aminotransferase elevations. Conservative wisdom has been to withhold statins if there is significant underlying liver disease, but the definition of "significant" is often left to the clinician's judgment and could include cirrhosis, chronic active hepatitis B or C, or nonalcoholic fatty liver disease (NAFLD).

To help with this dilemma, Chalasani et al[26] evaluated three groups of patients between January 1998 and June 2002:

- 342 hyperlipidemic patients with elevated baseline levels of AST (> 40 IU/L) or ALT (> 35 IU/L) who were prescribed a statin
- 1,437 hyperlipidemic patients with normal baseline AST and ALT levels who were prescribed a statin
- 2,245 patients with elevated baseline AST or ALT levels who were not prescribed a statin.

At 6 months, among the patients who had elevated aminotransferases at baseline who received a statin, the elevation had advanced to mild or moderate (defined as up to 10 times the baseline value) in 4.7%, and severe (more than 10 times the baseline value, or serum bilirubin greater than 3 mg/dL) in 0.6%.

Among those who had normal values at baseline who received a statin, the incidence of mild-moderate elevations (defined in this group as up to 10 times the upper limit of normal) was lower at 1.9% (P = .002), but there was no difference in severe elevations (AST or ALT more than 10 times the upper limit of normal, or elevated bilirubin): 0.2% (P = .2).

Comparing those with elevated baseline values who did or did not receive a statin, there were no differences in the incidence of mild-moderate (4.7% vs 6.4%, respectively, P = .2) or severe elevations (0.6% vs 0.4%, respectively, P = .6). The rate of statin discontinuation during the follow-up was similar whether or not patients had baseline ALT or AST elevations (11.1% vs 10.7%, respectively, P = .8).

The authors concluded that patients with elevated baseline aminotransferase levels are not necessarily at higher risk for hepatotoxicity from statin use.

If the patient has nonalcoholic fatty liver disease

NAFLD is a common clinical finding, affecting 10% to 24% of the general population in various countries. The prevalence increases with age, reaching a maximum between 40 and 49 years, and is strongly linked to obesity and the metabolic syndrome.[27] NAFLD is probably the most common cause of abnormal aminotransferase levels among adults in the United States.[28] Most patients have little change in liver function throughout the course of the disease. However, in a minority, histologic progression occurs, with a small fraction of them progressing to end-stage liver disease.

About 1% of patients on statins develop ALT or AST > 3 times the upper limit of normal

Many of the patients at high risk of coronary heart disease in clinical practice with obesity (body mass index > 30 kg/m^2), metabolic syndrome (as defined by the National Cholesterol Education Program), and diabetes who are candidates for statin treatment are likely to have NAFLD.

Whether statin treatment can adversely affect the histology of NAFLD was evaluated in a pilot study of five patients (four men and one woman; mean age 40 ± 8 years; mean body mass index 26.2 ± 2.5 kg/m^2) with biopsy-proven steatohepatitis.[29] None had elevation of aminotransferases to greater than three times the upper limit of normal. Pravastatin 20 mg/day was given for 6 months, and liver biopsy was repeated. Cholesterol levels declined significantly with treatment from 222 ± 40 mg/dL to 163 ± 28 mg/dL (P = .006), but not triglyceride levels (111 ± 69 vs 90 ± 40 mg/dL, P = .46). Liver enzyme levels normalized in all five patients. There was a variable degree of improvement in the grading of steatohepatitis but no change in the staging

TABLE 3

Managing muscle or laboratory abnormalities in patients receiving statins

PATIENTS BEGINNING STATIN THERAPY WITH BASELINE ELEVATIONS IN ALT OR AST (INCLUDING PATIENTS WITH CHRONIC LIVER DISEASE)

Measure baseline liver function, renal function, electrolyte levels, and thyroid-stimulating hormone levels before starting statin therapy

If they are known, involve consultants who have played a role in the evaluation of preexisting liver disease in the decision to start statin treatment

Consider nondrug causes of elevated aminotransferases (eg, infectious hepatitis, autoimmune hepatitis, excess alcohol use)

Consider if patient has nonalcoholic fatty liver disease and pursue evaluation to establish the diagnosis if necessary; this is not a contraindication for statin therapy if ALT or AST is < three times the upper limit of normal

After starting therapy, monitor ALT and AST at 6 and 12 weeks, and after each dose increase

If follow-up laboratory results show:

ALT or AST < three times the upper limit of normal:
- Continuation or advancement of statin is reasonable
- Monitor as suggested above

ALT or AST > three times the upper limit of normal:
- Confirm by repeat measurement within a week
- If abnormalities persist, consider dose reduction or stopping statin (especially in those with chronic liver disease or excess alcohol use)
- Repeat parameters in 2–4 weeks
- If parameters return to baseline on dose reduction, continue to monitor
- If statin was discontinued, consider rechallenge with the same or a different statin at a lower dose
- Continue surveillance and monitoring as outlined above

PATIENTS ON STATIN THERAPY WITH NEW ELEVATION IN ALT OR AST AND NO PRIOR LIVER DISEASE

If ALT or AST is < three times the upper limit of normal
- Review for new medication use and inquire about alcohol use
- Observe without change in dose; repeat parameters 6 weeks and 12 weeks after index test; if unchanged, continue with statin treatment, with cautious upward dose adjustment, if deemed necessary

If ALT or AST is > three times the upper limit of normal
- Consider nondrug causes of elevated aminotransferases (eg, infectious hepatitis, autoimmune hepatitis, nonalcoholic fatty liver disease) and pursue evaluation to establish diagnosis if necessary
- Review for new medication use and inquire about alcohol use
- Repeat measurements within a week; if abnormalities persist, consider reducing the dose or stopping the statin
- If aminotransferases improve after 2–4 weeks of dose reduction, continue to monitor
- If statin has been discontinued, consider rechallenge with a lower dose of the same statin or a different statin

score of fibrosis.

Another study[30] included 44 adult patients (24 men, 20 women) with biopsy-proven steatohepatitis. Those with normal lipid levels (n = 17) received ursodeoxycholic acid (UDCA) 13 to 15 mg/kg/day, while those with hyperlipidemia (n = 27) received atorvastatin 10 mg/day for 6 months. In the first group, serum and gamma-glutamyl-transferase (GGT) levels declined significantly; in the group receiving atorvastatin, serum cholesterol, AST, ALT, alkaline phosphatase, and GGT levels declined significantly. Liver densities increased only in the atorvastatin group, most likely due to diminishing fat content; normalization of aminotransferase levels was also more prevalent. The authors concluded that the use of atorvastatin in patients with nonalcoholic steatohepatitis with hyperlipidemia was effective and safe.

PATIENTS STARTING STATINS WITH ASYMPTOMATIC BASELINE CK ELEVATION

If CK is < three times the upper limit of normal
- Not a contraindication for starting statins
- Consider benign causes such as physical exercise, subclinical hypothyroidism
- Recheck CK at 6–8 weeks after starting statin; if unchanged, continue treatment

If CK is three to 10 times the upper limit of normal
- Consider other causes of CK elevation, including hypothyroidism and inflammatory muscle disorders
- Check for muscle weakness
- Review if patient is on other potentially myotoxic drugs, or ones that may interact with statins
- May initiate statin therapy at a low dose, with repeat CK measurement in 4–6 weeks
- Stop statin immediately if symptoms of myalgia or weakness develop or if CK elevation is > 10 times the upper limit of normal

If CK is > 10 times the upper limit of normal
- Evaluate or refer patient to determine cause of myositis
- Statin therapy can be initiated at low dose, after careful evaluation for etiology of myositis and consideration of coronary heart disease risk

PATIENTS ON STATINS WITH NEW CK ELEVATIONS

Without symptoms

CK < three times the upper limit of normal
- Continue statin therapy
- Rule out benign causes such as strenuous exercise, subclinical hypothyroidism
- Ensure that there is no weakness on history and physical examination
- Recheck CK in 6 weeks

CK three to 10 times the upper limit of normal
- Rule out other causes of CK elevation (as above)
- Review if patient is on other drugs known to interact with statins
- Ensure that there is no weakness on history and physical examination
- Consider reducing the dose or stopping the statin

CK > 10 times the upper limit of normal
- Stop statin therapy
- Evaluate or refer patient for workup of myositis

With symptoms
- Establish severity and extent of muscle symptoms
- Stop statin immediately if patient has muscle weakness or severe pain with dark urine
- Obtain an urgent CK measurement:
  - If < three times the upper limit of normal, follow algorithm as given above, provided patient's symptoms are deemed tolerable
  - If > three times the upper limit of normal, stop statin, repeat CK in 7 days, and if stable, repeat 6 weeks later
  - If CK is normalized, consider rechallenge with lower dose of same or another statin
  - If > 10 times the upper limit of normal, stop statin, and evaluate clinically for muscle weakness, and for renal function and urine myoglobin
  - Hospitalize if the patient has renal insufficiency, and start urine alkalinization

ALT alanine aminotransferase; AST aspartate aminotransferase; CK creatine kinase

We believe that NAFLD is not a contraindication to statin use if the ALT and AST levels are less than three times the upper limit of normal.

CLINICAL MANAGEMENT OF STATIN-RELATED EVENTS

In 2002, the ACC/AHA/NHLBI Clinical Advisory Group[7] summarized the current understanding of the appropriate use and safety of statins. Using available clinical trial data and peer-reviewed literature, they affirmed that the risk of increases in ALT to more than three times the upper limit of normal is very low for all statins (< 1%) and is dose-related. The risk of myositis, with CK values greater than 10 times the upper limit of normal, is also very low (< 0.5%), with the incidence of rhabdomyolysis being even lower (< 0.1%).

The Advisory Group recommends that aminotransferase levels be measured in all patients before starting statin therapy. Modest aminotransferase elevations (less than three times the upper limit of normal) are not thought to pose a contraindication to starting, continuing, or advancing statin therapy, as long as patients are carefully monitored.

However, it is less clear if CK levels should be routinely measured before starting treatment. Some experts argue that mild asymptomatic CK elevations are common and that pretreatment knowledge of this can aid in subsequent clinical decision-making.

While statin-induced side effects can be idiosyncratic, the Advisory Group notes that they are usually predictable and are more likely to happen in certain clinical situations. The advisory report provides a checklist that physicians should consult before initiating statin therapy (TABLE 2).

RECOMMENDATIONS FOR CLINICIANS

Statin therapy has been very successful in reducing the incidence of major coronary events, coronary procedures, and stroke in patients at high risk. This potential has not yet been fully realized, however, because many patients at heightened risk do not stay compliant with therapy. Nevertheless, continuing advances in medical research are likely to establish broader roles for statins in treating and preventing other diseases.

Clinical judgment is the most important component of our recommendations

Specific groups at higher risk

Statins are generally safe, provided that care is taken in specific groups of patients in whom adverse reactions are more common, eg, those who:

- Are older (> 70 years) and frail, particularly women
- Have multisystem diseases such as heart failure and renal insufficiency
- Are receiving immunosuppressive drugs such as cyclosporine
- Are receiving higher doses of a statin. For this reason, physicians should not exceed doses necessary to achieve a patient's lipid goals.
- Are receiving multiple drugs, including drugs known to interact with statins. A careful review is mandated whenever a new drug is added to the regimen. Although grapefruit juice may inhibit statin metabolism, this occurs at quantities of nearly a quart or more per day, which most patients rarely consume.

Regular laboratory surveillance is key to monitoring patients at high risk of muscle and liver adverse effects. Keeping these caveats in mind, we summarize in TABLE 3 our recommendations for patients with biochemical or symptomatic muscle or hepatic abnormalities or both, emphasizing care both for patients who have never received a statin before and for those established on statin therapy. Of course, clinical judgment is the most important component of how to use our recommendations.

We hope that these clinical recommendations about managing the biochemical measures of muscle and/or hepatic adverse effects of statins will allow practicing physicians to comfortably prescribe these lifesaving medications, while ensuring patient safety. Careful and prudent clinical judgment and periodic laboratory surveillance will maximize the benefit of statins with minimal risk.

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