

Statins and elevated liver tests: What's the fuss?

Even when liver function tests are moderately elevated, statins are safe for most patients

Edward Onusko, MD
 Clinton Memorial Hospital/
 University of Cincinnati Family
 Medicine Residency Program,
 Wilmington, Ohio
 edonusko@cmhregional.com

Practice recommendations

- Order liver function tests before starting statin therapy, 12 weeks after initiation, with any dose increase, and periodically for long-term maintenance therapy (C).
- Mild elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (<3 times the upper limit of normal [ULN]) following statin therapy do not appear to lead to significant liver toxicity over time (C).
- Other medications that lower low-density lipoprotein (LDL), and might be substituted for statins, may not improve morbidity and mortality (C).

Strength of recommendation (SOR)

- A Good-quality patient-oriented evidence
 B Inconsistent or limited-quality patient-oriented evidence
 C Consensus, usual practice, opinion, disease-oriented evidence, case series

Are we more aggressive than ever when it comes to our use of statins? You bet.

Should this prompt a heightened attention to hepatic safety? In a word, no. The more detailed, evidence-based answer (which follows) makes 2 things clear:

1. Clinically significant hepatic injury following statin use is very rare.
2. While US Food and Drug Ad-

ministration (FDA) labeling recommends routine monitoring of serum transaminase levels prior to and during statin therapy, the evidence suggests that such routine monitoring is not clinically necessary.

More potent statins, more combination therapy

Our prescribing has become more aggressive to keep pace with National Cholesterol Education Program (NCEP) recommendations. In 2001, the NCEP Adult Treatment Panel III indicated:

- LDL cholesterol should be the primary target of therapy.
- The LDL cholesterol goal should be based on the patient's risk of cardiovascular disease.
- Statins are the most effective agents to achieve treatment goals.¹

Three years later, the NCEP advised that in light of more recent clinical trials, even more aggressive (ie, lower) LDL goals should be considered for patients at very high risk, high risk, and moderately high risk for cardiovascular disease.²

As a result, we are prescribing higher doses of statins, more potent statins, and more combination therapies of statins with other lipid-altering agents. Not surprisingly, this trend has prompted

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Treat fatty liver disease with statins?

An interesting clinical question is whether statins are appropriate when the cause of hepatic enzyme elevation appears to be excess fat in the liver. There is some evidence that treatment of fatty infiltration of the liver may lower transaminase levels and improve histological findings.¹⁴ In general, though, no medications have been demonstrated to improve patient-oriented outcomes such as mortality or need for liver transplant.¹⁵

concerns about the potential increase in toxicities/side effects of statins.

This review examines the hepatic safety profile of statins and details why there's no need to stop treatment based on moderate elevations in liver function tests. The most common serious side effect of statins—muscle damage/rhabdomyolysis—is rare, and is not extensively discussed here.

■ Clinical trials: Risk is small

A review of 35 randomized clinical statin trials reported from 1966 to 2005, involving 74,102 patients, reported an absolute risk of transaminase (also referred to as aminotransferase) elevations from statin therapy of only about 4 per 1000 patients (risk difference [RD]=4.2; 95% confidence interval [CI], 1.5-6.9).³ The same researchers' analysis of 28 clinical trials involving 62,184 patients showed a relative risk of increased transaminase of 1.3 (95% CI, 1.06-1.59), achieving statistical significance only for the fluvastatin and lovastatin trials.³

High-dose statin therapy. A review of clinical trials involving high-dose statin therapy found rates of hepatic enzyme elevation (defined as ALT or AST >3 times the ULN on 2 or more consecutive occasions) to be quite low (<1.3%).⁴ Higher statin doses were more likely to increase enzyme levels, though reduction in the dose or withdrawal of the statin resulted in normalization of the liver enzymes.

A study of patients ages 65 to 85

years who were treated with high-dose atorvastatin (80 mg per day) vs moderate dose pravastatin (40 mg per day) resulted in only 11 of 893 (1.23%) patients discontinuing the drug following abnormal liver function tests; most of these were in the high-dose treatment arm.⁵

■ Small risk in clinical practice, too

Clinical trials often have lower rates of adverse effects from medications than are seen in usual clinical practice.⁶ This may be because the stringent application of patient selection and exclusion criteria used in the administration of clinical trials does not occur in the "real world."

However, the FDA database reported only 0.69 cases of hepatitis/liver failure per million statin prescriptions through 2004.⁴ A retrospective review of 1194 patients treated with a statin showed that 85% (1014) of patients had at least 1 monitoring test of transaminases performed during the year of the study. Of these, 10 (1.0%) had a significant elevation and 5 (0.5%) had a moderate elevation of transaminases. A review of the patient records demonstrated that none of these abnormalities appeared to be related to the use of statins, suggesting that routine monitoring of transaminases with statin therapy is not clinically necessary.⁷

A retrospective review over a 5-year period of 23,000 patients receiving statins in a large health maintenance organization found that only 17 (0.1%) patients had severe elevations of ALT (defined as >10 times the ULN). Of those 17 patients, 13 cases were associated with drug-drug interactions, and all but 1 resolved with discontinuation of the statin.⁸

■ What to monitor, how often

Product labeling for all statins advises measurement of transaminases (AST as well as ALT), although some liver experts would recommend ALT alone. ALT is found primarily in the liver, while

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Clinical trials involving high-dose statin therapy reveal that rates of hepatic enzyme elevation are quite low (<1.3%)

AST is also found in muscle (cardiac and skeletal), kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. AST is, therefore, less specific for hepatic damage than ALT.

Routine monitoring of other liver function tests that measure the liver's transport ability (eg, bilirubin, alkaline phosphate) or synthetic ability (eg, albumin, prothrombin time) will increase the likelihood of false-positive results and increase expense; they should not be done.

The 2002 American Gastroenterological Association guidelines recommend that for any hepatotoxic drug, if the ALT and/or AST elevations are <5 times the ULN, the drug should be stopped and the enzymes rechecked after an appropriate interval before pursuing a more extensive evaluation for liver disease.⁹

The FDA labeling information for all statins recommends liver function testing before putting a patient on a statin, 12 weeks after initiation, at any dose increase, and "periodically" for long-term maintenance therapy (TABLE 1).¹⁰ These recommendations are based on expert opinion only, because most data suggest that significant liver damage from statins is very rare and that routine monitoring of liver enzymes is not necessary.

The ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins agrees with the FDA, although it specifies "periodically" to mean annually.¹¹

■ It's difficult to predict hepatic effects

Individual statins vary as to potency, efficacy, metabolism, and drug interactions. However, the exact mechanism of how statins cause elevations of ALT and AST is unknown, making it difficult to predict the hepatic effects of an individual statin based on its characteristics.

One analysis of multiple clinical trials concluded that overall statin toxicity (muscle, liver, etc.) was not directly related to the degree of lowering LDL cholesterol; instead, it correlated with the dose

TABLE 1

When to monitor liver function in patients taking statins^{10,11}

WHEN TO CHECK ALT/AST	WHAT TO DO
Initiation of treatment or increase in dose	Begin/increase dose of statin if ALT and AST are <3 times the ULN
12 weeks after initiation of statin therapy	Discontinue the statin (or lower the dose) if ALT or AST are >3 times the ULN
Long-term (annually or "periodically")	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

of the statin.¹² As seen in TABLE 2, statins have variable drug-drug interactions based on their metabolism by the cytochrome P450 system. Drugs that increase the level of a statin in the blood may potentially increase the risk for toxicity and may warrant more cautious monitoring of liver enzymes, but are not necessarily contraindications to statin therapy.

Cyclosporine, macrolide antibiotics, azole antifungal agents, and other cytochrome P450 inhibitors (TABLE 2) are among the relative contraindications to the use of statins, more for concerns about myopathy than hepatotoxicity.¹ If these medications are used with a statin, consider more frequent monitoring of transaminases.

■ Discontinue the statin?

ACC/AHA/NHLBI recommendations indicate that you should discontinue (or lower the dose of) statin therapy if the ALT or AST are above 3 times the ULN on 2 consecutive occasions.¹¹ When elevations of ALT or AST are <3 times the ULN, consider the following:

- Statins have rigorously proven benefits for preventing morbidity and mortality due to atherosclerotic cardiovascular disease. A meta-analysis of more than 70,000 patients concluded that the number needed to treat to prevent 1 cardiovascular event was 27 and the number needed to harm (NNH) was 197. For more serious events such as creatine kinase >10 times the ULN, the NNH was

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The FDA reported only 0.69 cases of hepatitis/liver failure per million prescriptions for statins

TABLE 2

**Statin snapshot:
LDL reductions to expect, interactions to avoid**

	LOVASTATIN (MEVACOR, GENERICS)	PRAVASTATIN (PRAVACHOL, GENERICS)	SIMVASTATIN (ZOCOR, GENERICS)	FLUVASTATIN (LESCOL, GENERICS)	ATORVASTATIN (LIPITOR)	ROSUVASTATIN (CRESTOR)
Usual daily dose	20 to 80 mg	40 to 80 mg	10 to 80 mg	20 to 80 mg	10 to 80 mg	10 to 40 mg
LDL reduction	27% to 42%	34% to 37%	30% to 47%	22% to 35%	39% to 60%	52% to 63%
% protein binding	>95%	50%	95%	98%	>98%	88%
Cytochrome P450 metabolism	3A4*	None	3A4*	2C9 (75%)† 2C8 (5%) 3A4 (20%)	3A4*	Limited 2C9 (10%)

*Drugs that may significantly increase statin levels via competitive metabolism or inhibition of CYP3A4 enzymes include macrolide antibiotics, HIV protease inhibitors, azole antifungal agents, calcium channel blockers, fluoxetine, cimetidine, cyclosporine, and omeprazole. Grapefruit juice may also have this effect.

†Drugs that may significantly increase statin levels via interference with CYP2C9 enzymes include phenytoin, glyburide, cimetidine, omeprazole, diclofenac, and cyclosporine.

Source: Physicians' Desk Reference. 2008. 62nd ed. Montvale, NJ: Thomson PDR; 2008.

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Cyclosporine and macrolide antibiotics are relatively contraindicated in statin use—more for concern of myopathy than hepatotoxicity

3400. Rhabdomyolysis alone was rare with a NNH of 7428.⁴

- Other medications that lower LDL and might be substituted for statins may not improve morbidity and mortality. For example, a recent clinical trial of ezetimibe (Zetia) reminds clinicians to be cautious in assuming that treatments that improve biochemical parameters such as LDL will necessarily result in improved clinical outcomes.¹³

- Mild elevations of ALT or AST (<3 times the ULN) following statin therapy are not known to lead to any significant liver toxicity over time.

- To date, there are no randomized controlled trials evaluating the optimal management of liver enzyme elevations with statin therapy. ■

Correspondence

Edward Onusko, MD, Family Health Center, 825 W. Locust, Wilmington, OH 45177; edonusko@cmhregional.com.

Disclosure

The author reported no potential conflict of interest relevant to this article.

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