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# The Myth of Statin-Induced Hepatotoxicity

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Statin-induced hepatotoxicity is a myth. "Myth" is used here to mean a false collective belief that, despite factual contradiction, endures as suspicion. The legend asserts that isolated alanine aminotransferase (ALT) elevations associated with statin therapy are harmful and must be avoided. How did this fable arise? The Fogarty conference proposed in 1978 that an ALT value more than three times the upper level of normal (ULN) was "markedly abnormal" and should be used as an indicator for drug-induced liver injury. Not a shred of proof was offered for this recommendation. This arbitrary measure became a standard for monitoring drugs in clinical trials (1). In the 1980s, trials of hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, known as statins, were just getting started. Since then, statins have been observed to cause mild ALT elevations in 10% of recipients, and in 1–3% of patients the elevations are more than three times the ULN (2).

ALT testing is not specific to the liver; it was first discovered as a marker for acute myocardial infarction in 1955 by Arthur Karmen. Many organs, such as the heart, muscle, and kidney, need to transfer amino acids to link protein and carbohydrate metabolism. The liver is not responsible for regulating the plasma activity of aminotransferases, whose levels are the net result of release and degradation of enzyme from many organs.

Is an isolated ALT elevation greater than three times the ULN a marker of statin-induced liver injury? No. A lovastatin vs. placebo trial with a median follow-up of 5 years randomized 6,500 subjects to drug and placebo. The number of patients who developed ALT elevations greater than three times the ULN did not differ between lovastatin and placebo (18 (0.6%) vs. 11 (0.3%)) (3).

The Scandinavian Simvastatin Survival Study enrolled more than 2,200 placebo recipients. Patients developing an ALT level greater than three times the ULN did not differ between the simvastatin and placebo groups (14 (0.7%) vs. 12 (0.6%)). In two other controlled studies of simvastatin, no patient emerged with persistent liver test abnormalities following the initial 6 months of treatment at a given dose (4). Another placebo-controlled trial, with 20,536 participants over 5 years with 40 mg simvastatin, found no hepatitis in either group. The latter investigators concluded that "routine monitoring of liver function tests during treatment with simvastatin 40 mg is not useful" (5).

For pravastatin, more than 19,000 patients were randomized to drug or placebo in three trials. Again, marked abnormalities of ALT or aspartate aminotransferase (AST) occurred with similar low frequency with pravastatin or placebo (≤1.2%) (6).

A 2.5-year database survey in the United Kingdom did not show any cases of acute hepatitis in 10,289 users of rosuvastatin. The definition of acute, not infectious or alcoholic, hepatitis in this latter study was based on an American College of Cardiology guideline stated as "a clinical diagnosis of hepatitis requiring hospitalization, with levels of serum ALT elevated to >three times the ULN" (7).

Atorvastatin is also without significant hepatotoxicity (8).

Finally, in two placebo-controlled trials with 2,106 patients, fluvastatin was found to have a 1.13% incidence of liver test abnormalities vs. 0.29% with placebo ($P$ = 0.04) (9). However, the incidence of changes in the placebo groups was exceedingly low, whereas the observed incidence with fluvastatin was similar to that with other statins.

Elevation of serum ALT is not a disease. At worst, the ephemeral out-of-range ALT values represent adaptation to exposure to statins by the different organs involved in ALT regulation. In the liver this is done by alteration of metabolic enzyme and transporter systems to process the drug. When a statin is continued, despite elevations of ALT, the ALT eventually returns to normal unless some other cause for liver disease exists (4,10,11).

At best, the temporary increase in ALT may be merely the result of lowering cholesterol and not a sign of tissue effect. Indeed, there is up to a 3% incidence of transient, reversible elevations of ALT that are characteristic of all the lipid-lowering agents, including bile acid sequestrants, fibric acid derivatives, and nicotinic acid (11).

Apart from asymptomatic ALT elevations, the development of a chronic liver disease, such as that seen with isoniazid, has not been seen. Moreover, no consistent liver biopsy picture has arisen to represent potential statin-induced hepatotoxicity (2).

It has been difficult to determine the overall incidence of acute liver failure (ALF) in the United States. One estimate determined the idiopathic ALF rate to be from 0.5 to 1.0 cases per million, and the incidence of possible statin-induced ALF to be 0.2 cases per million (11). Thus, one cannot tell whether statins are involved in ALF because of background noise. This is especially true when 10% of the adult population is taking statins, since, when a case of idiopathic ALF arises, 1 in 10 will be taking a statin by chance alone.

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**Table 1. Summary of changes in liver-test recommendations on US Food and Drug Administration package inserts**

| Statin | Older package insert | Current package insert |
|---|---|---|
| Lovastatin | (2001) LFTs before and at 6 and 12 weeks after start or elevation of dose and semiannually | (2009) LFTs before initiation of therapy in those with a history of liver disease or when otherwise clinically indicated |
| Simvastatin | (2000) LFTs before treatment and semiannually for first year or until 1 year after last elevation | (2008) LFTs before treatment and then when clinically indicated |
| Pravastatin | (2001) LFTs before initiation of therapy, before elevation of dose, and when otherwise clinically indicated | (2007) LFTs before initiation of therapy and when otherwise clinically indicated |
| Fluvastatin | (2001) LFTs before and at 12 weeks after the initiation of therapy and any elevation of dose | (2009) No change |
| Atorvastatin | (2001) LFTs before initiation of therapy, after elevation of dose, and semiannually | (2009) No change |
| Rosuvastatin | (2003) LFTs before and at 12 weeks after the initiation of therapy and any elevation of dose and periodically (e.g., semiannually) thereafter | (2009) No change |

Labels available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
LFT, liver-function test.

Finally, most hepatologists no longer consider statins to have any significant hepatotoxicity. A national panel of liver experts concluded that aminotransferase elevations associated with statin therapy are not evidence for liver damage or dysfunction (12).

What about giving statins to patients with liver disease? Hyman Zimmerman, author of the first book on drug-induced hepatotoxicity, stated, "A stubborn misconception regarding susceptibility to hepatic injury has been the view that patients with preexisting liver disease are more likely than others to experience hepatic injury on exposure to drugs that cause liver damage" (13).

Statins may even confer benefit in certain liver diseases. Randomized controlled trials of statins have been started in nonalcoholic steatohepatitis (NASH) after two case series with NASH patients have shown histological and liver test improvements (14,15).

Our group has shown uniform improvement of abnormal ALT levels in patients infected with hepatitis C virus (HCV) who have elevated ALT when the statin is started (16). We have also shown anti-HCV activity of fluvastatin in chronic carriers of HCV in whom treatment with peginterferon/ribavirin had failed (17). Three retrospective studies have shown an increased sustained viral remission rate of HCV when statins were taken during peginterferon/ribavirin treatment (18–20).

Simvastatin may become useful in the treatment of portal hypertension. Abraldes and colleagues have extensively investigated simvastatin as an agent to treat portal hypertension (21). They recently reported a 30-day double-blind randomized controlled trial using 20–40 mg/d of simvastatin in 59 patients with advanced cirrhosis and portal hypertension (wedged hepatic venous pressure ≥12 mm Hg). A significant lowering of portal hypertension (−8.3%) as measured by hepatic venous pressure gradient was noted (22).

I am not suggesting that statins are ready to be recommended for treatment of liver diseases but raise the topic to help turn the tables about the suspicion of harm. Most physicians "know" statins cause hepatotoxicity because the package inserts contain warnings about this problem. When I discussed the lack of evidence of hepatotoxicity of statins with a high-ranking US Food and Drug Administration (FDA) official (who asked not to be quoted), the official replied that the FDA is no longer concerned about statins causing hepatotoxicity. When I asked why the package inserts still contained the language, I learned that only the manufacturer can request a label change and the FDA can then consent to the change; the agency cannot unilaterally delete language on a package insert.

Nonetheless, the FDA has responded positively to manufacturers by agreeing to the omission and watering down of the language about ALT monitoring for the generic statins lovastatin, simvastatin, and pravastatin (**Table 1**). The most dramatic change has occurred with lovastatin, for which liver-function monitoring is no longer requested for asymptomatic patients without a history of liver disease.

One might contemplate that it would be better to continue ALT monitoring in order to detect any possible damage that might exist. However, the continued myth of statin hepatotoxicity causes real harm on individual, group, and financial levels.

As one example, an endocrinologist asked me, a board-certified transplant hepatologist, to see a 47-year-old man with familial hypercholesterolemia. The patient had recently suffered a myocardial infarction, and his low-density lipoprotein (LDL) was 450 mg/dl (11.6 IU). The only therapy that lowered this patient's LDL below 200 mg/dl (5.18 IU) was statin treatment. Yet the cardiologist was adamant that the statin be stopped for fear of hepatotoxicity because the ALT was minimally out of range at 61 IU/l. It took some persuasion by the endocrinologist and me to convince the cardiologist that the benefit/risk ratio for the statin was greatly in favor of continuing the statin.

Although no systematic study exists of the number of patients whose statin use is discontinued permanently because of elevated ALT, it is a practice that I commonly encounter. One could estimate that

**Table 2. Cost assumptions for liver-function testing during statin use**

| |
|---|
| Number of people in the United States taking statins in 2005[a]: 30 million |
| Cost of liver-function test[b]: $50 |
| Cost per year of semiannual tests[c]: 30,000,000 × $50 × 2 = $3,000,000,000 |

[a]From 2000 to 2005, statin use doubled. The number of persons taking statins in 2010 is probably far greater. [b]Costs vary from $12 to $99; $50 was chosen as average. [c]According to package inserts (see **Table 1**). This does not include tests performed before initiation of statin use and at 12 weeks after start as recommended in several package inserts.

1–10% of those taking statins (i.e., 300,000 to 3,000,000) have been denied the benefit of statins as a result of unwarranted concern (23).

Group harms occur when patients with liver disease are denied statins. This is illustrated by the recent report that only 2% of HCV patients in the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) trial ($n$ = 3,070) received statins, when by current LDL guidelines 38% should have been on statins (S. Harrison, personal communication) (20).

In 2005, 30 million people in the United States were taking statins—double the number in 2000. The cost of semiannual liver test monitoring is conservatively estimated to be $3 billion a year (**Table 2**) (23,24). Although it is likely that physicians do not comply well with these package insert guidelines, whatever fraction of this number is chosen by the reader still represents a substantial amount. Given the current medico-political climate, savings by eliminating unnecessary tests are a priority.

The most effective way to dispel the myth would be to allow the FDA a regulatory mechanism to allow removal of outdated language—a sort of "black box" in reverse. In the meantime, various medical guidelines could promulgate freedom from liver test monitoring.

It is much more difficult to prove safety than efficacy. The passage of time and the number of prescriptions given may represent the best test of safety. Statins have been on the market for more than 22 years, with literally billions of pills taken. If there were patterns of liver damage caused by statins, these would surely have been seen by now.

## CONFLICT OF INTEREST

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