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The Statin Hepatotoxicity Myth

Statins have been on the market for more than 22 years and literally billions of pills have been taken. No patterns of liver damage have been identified but because of the package inserts most physicians believe statins precipitate liver damage. There is no data to support this assumption!

Background Story: In 1978, National Institute of Health Guidelines decreed 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]

GREACE Study: An excellent and groundbreaking study published online in Lancet last month showed *uniform improvement of high abnormal liver-function tests (LFTs)* in patients after they were started on statins.[3] These results match those of two other recent studies in patients with Hepatitis C—showing uniform improvement of LFTs.[4] [5] What makes this particular study special is that it is the first to show statins' *additional benefit of reducing cardiovascular (CV) events* in patients with abnormal liver-function tests in addition to improving LFTs. The study included only patients with LFT elevations less than 3x normal who were assumed to have fatty livers or non-alcoholic steatohepatitis (NASH). The patients with the higher LFTs had the most CV benefit. In patients who did not receive statins LFTs increased or stayed the same and they obviously didn't get CV benefits.

What's all the Fuss? The FDA database reported only 0.69 cases of hepatitis/liver failure per million statin prescriptions through 2004. A retrospective review of 1194 patients treated with a statin showed that 85% (1014) of patients had at least 1 monitoring test of LFT (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 LFTs. 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 LFTs with statin therapy is not clinically necessary.[6]

Unwarranted Concern: Statin-induced hepatotoxicity is a myth. Four large trials of statins have shown no difference in the frequency or degree of LFT increases between treatment and placebo groups (involving greater than 48,000 patients). Out-of-range values, which do occur with statin use, eventually return to normal even if the same statin is continued. The occurrence of acute liver failure thought to be caused by statins is well below what is now understood as the background rate of idiopathic acute liver failure in the general population. No consistent liver biopsy picture from possible statin-related drug injury has emerged, and there are no reports of chronic carriers of drug-induced liver damage from statins. Thus, an increased ALT in this situation is not a

disease. Despite the absence of liver injury from statins, a US survey showed that 50% of academic physicians would be reluctant to give a statin to a patient who presents with an ALT of more than 1.5 times the upper limit of normal. More than 40% would deny a statin to patients with chronic hepatitis C, another 2% of the general population.[7]

Statin Under-treatment: No studies are available to show how many patients are denied statins because of pre-existing changes in liver-function tests, or how many patients have statins discontinued when ALT increases. But we do know that 10% of patients who take statins develop elevated LFTs. One percent of those develop LFTs 3x normal. Another 20% or more of people in developed countries have either fatty liver or NASH and most of these people have elevated LFTs at some time or another. This suggests that 10 to 30% of people might fall into these categories, and would therefore be denied a statin. If so, this large group represents a substantial source of CV disease which is not being prevented with use of proven safe statin therapy, because of an unproven package insert.

Further harm ensues from the cost of monitoring with liver-function tests. One conservative estimate has the US cost of monitoring LFTs at 3 billion dollars per year (Table 1 below).[8]

Table 1. Cost assumptions for LFTs during statin use

Number of people in the United States taking statins in 2005: 30 million
Cost of liver-function tests: $50
Cost per year of semiannual tests : 30,000,000 x□$50 x□2 = $3,000,000,000
From 2000 to 2005, statin use doubled. The number of persons taking statins in 2010 is probably far greater. Costs vary from $12 to $99; $50 was chosen as average.

*This does not include tests performed before initiation of statin use and at 12 weeks after start as recommended in several package inserts.

Given the present healthcare-financial climate, cost-saving by eliminating unnecessary tests should be a priority.

Conclusions:

A smart man once told me, "In order to sway someone to your way of thinking you have to give them adequate reason to do so".

- We should not deny indicated statin therapy to a patient with elevated LFTs. The data is clear with regard to LFTs less than 3x normal.
- It's time to dispel the myth of statin hepatotoxicity.
- LFT's aren't necessary unless patients have pre-existing history of liver disease.

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