

## Yes! Statins can be given to liver patients

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Statins are given to 10–20% of adults in developed countries. Statins increase alanine aminotransferase (ALT) concentrations in 10% of patients without liver disease, and this increase can exceed more than three times the upper limit of normal in 1% of such patients. In contrast, we will note that this ALT escalation does not appear to occur when statins are initiated in patients with fatty liver or hepatitis C.

In the field of drug-induced liver disease, attempts are made to distinguish between medicines that cause hepatotoxic reactions and idiosyncratic reactions. The principal differences are that hepatotoxic reactions are dose dependent and predictable (e.g., acetaminophen); while idiosyncratic reactions are not dose dependent or predictable (e.g., penicillin). Do statins cause liver injury? This author has asserted with voluminous supporting data that statins are not hepatotoxic [1].

Do statins cause rare idiosyncratic drug reactions? Probably. In this issue, Bjornsson *et al.* present an epidemiological survey of a monitoring system using RUCAM methodology to discover drug toxicity [2].

The strengths of their work are the authors' experience, the 22 years of observation, and that the database is limited to a single country, Sweden. The report is fortified by their addition of drug rechallenge cases, though drug rechallenge is not the gold standard it was once thought. Positive rechallenge cases have sometimes been discovered to accidentally take the identical drug on a subsequent date without a problem; conversely, negative rechallenge cases sometimes experience a similar idiosyncratic reaction later on the same drug. The problem lies partly in cross reactivity of chemical moieties. The sensitivity and specificity of a drug rechallenge to determine the cause of an idiosyncratic reaction is poorly understood [3].

The weakness of the study is the reliance upon the Roussel Uclaf Causality Assessment Method (RUCAM). RUCAM is a scoring method that attempts to quantify clinical judgment. Amongst a multitude of problems, the RUCAM suffers from a high degree of interobserver variability [4,5]. Moreover, it is prejudicial against statins by begging the question. That is, RUCAM scoring assigns two points for a drug-induced liver reaction if the product label contains a liver injury notation. As I have noted elsewhere, the product labels of statins are terribly outdated with liver

injury warnings that have no data to support them [1]. Thus, when one looks even at the rechallenge cases by Bjornsson *et al.* (Table 1, column 4) and then subtracts 2 points from each case because of circular reasoning, the interpretation of final scoring might move from "highly probable" to only "probable".

While efforts are being made to improve the accuracy of RUCAM [5], the positive predictive value of a method which is 89% specific for a condition that occurs once in every 100,000 cases is far less than 1%. Thus, there is still legitimate doubt that these cases truly represent statin related idiosyncrasies. In defense of the authors, this was the best method available for this inquiry; but it serves to point out the immaturity of the field of drug-induced liver disease. What is needed in the field is the application of solid science using drug protein adducts and pharmacogenomics.

The determined frequency of liver injury, 1/100,000 users, may be an overestimate since others have suggested a prevalence of 1/1,000,000 [6]. Moreover, an internal comparison suggesting this article overestimates the frequency of idiosyncratic liver reactions to statins is that this is the first report the author is aware of for which this effect on the liver occurred more often than severe muscle injury. Usually, myopathy is a more common side-effect than idiosyncratic liver damage. The authors recognize this inverted aspect of their findings, but have no ready explanation.

Whether or not statins cause acute liver failure has still not been determined. It has been difficult to ascertain the overall incidence of acute liver failure (ALF) in the United States. This reviewer has no information for the rate of idiopathic ALF in Scandinavia. Tolman estimated the idiopathic ALF rate in the USA 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 [7]. The rate in the current study appears to be around 1 per million and thus one cannot tell whether statins are involved in ALF due to background noise.

Regardless, this report of idiosyncratic drug reactions needs to be put into perspective.

In large 5–10 year trials, statins prevent about 33% of major cardiovascular events when compared to placebo. In other words, the number needed to treat (NNT) is 3. If statins cause serious liver disease, it is on the order of 1/100,000 to 1/1000,000. The number needed to harm (NNH) is about 1 million. Estimates of patients who fail to receive statins out of fear of hepatotoxicity range from 10% to 30% [1]. Thus, the anxiety over this possible drug reaction, which if it exists is extremely rare, causes

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## Editorial

thousands of patients to needlessly suffer fatal cardiovascular events. My advocacy stems from the frustration of liver transplant candidates who are denied listing because of advanced coronary artery disease; patients who may have been eligible for listing had they been put on a statin in a timely manner. The literature shows that from 7% to 29% of liver transplantation candidates are denied listing due to coronary disease [8].

What about prescribing statins for patients with liver disease and cardiac risk factors?

Dr. Zimmerman, the late doyen of drug-induced liver injury, reminded us: "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" [9].

Hepatologists in Europe and the United States have a bias against using statins in patients with liver disease who have hypercholesterolemia [1]. A more recent trial in 403 patients with hepatitis C reported statin use in only 12 patients [10].

Fatty liver is by far the most common liver disease encountered. We are doing a distinct disservice by not prescribing statins for this group. Why? The prospective Cremona study from Italy, a 15 year follow-up of patients with fatty liver, has shown us that these patients are seven times more likely to die of cardiac disease than liver disease [11].

Athyros *et al.* reported data from a Greek randomized trial of the efficacy and safety of statins in patients with baseline increases of ALT that were less than three times the upper limit of normal. All of these patients were thought to have fatty liver. In patients with fatty liver, serious increases of ALT occurred no more often than in a similar group who were not given statins. Moreover, ALT improved or normalized in patients who were given statins, whereas in the group not given statins, liver tests continued to worsen. Most importantly, patients who started the trial with elevated liver tests derived the greatest cardiovascular benefit of any group – a favorable effect (50%), which was substantially greater for these patients than for patients who started statins with in-range liver tests! The uniform improvement in liver tests for fatty liver patients noted by Athyros *et al.* matches our observations in patients with hepatitis C who are given statins [12,13].

Space limits a discussion of all liver diseases. Extensive data exist as to cardiac mortality in HCV and HBV. Hepatitis C confers a significant increase in cardiovascular disease mortality both in the USA and United Kingdom [14,15]. On the other hand, patients who are positive for hepatitis B surface antigen have neither an increased or decreased risk of cardiovascular disease [14,15].

We have shown no elevation of ALTs in more than 100 HCV patients prospectively given statins for periods of up to 72 weeks (unpublished and [16]). Others have had the same experience in over 200 HCV patients [17,18]. Moreover, we and others have documented uniform improvements in ALT values in HCV patients given statins [19,20].

We have preliminary data in 13 HBV patients. HBV patients neither increase nor decrease their ALT values when given statins prospectively (unpublished). Surely, with HBV infection being the most common chronic infectious disease worldwide (400 million carriers), it is quite likely that millions of patients have been given statins accidentally over the past 23 years without reports of special hepatotoxicity.

However, in contrast to fatty liver disease, the author is unaware of any long-term cardiovascular prevention trials with stat-

ins in patients with HBV or HCV; such trials have usually excluded patients with liver disease. Nonetheless, there is no reason to suspect that statins would have any diminished efficacy.

Does monitoring with ALT tests help to predict this rare injury? No.

The authors end their current report with wise counsel: "Responsible physicians should measure liver tests in patients taking statins with newly developed symptoms such as nausea, severe lethargy and abdominal pain." I agree. This is the same approach shown useful in detecting severe cases of INH toxicity in early stages. ALT monitoring for statins does more harm than good by discovering the irrelevant finding of 1 in 10 patients who will elevate their ALT level; elevations that will return to normal even if the same statin is continued.

Billions of dollars are spent on useless monitoring of ALT enzymes during statin therapy that could be used for much better health care purposes [1]. But the worst side effect of this misleading monitoring is the terrible cost in human life by frightening physicians and patients away from the cardiac prevention potential of statin use.

A problem of interpretation could arise when a patient experiences a flare of their intrinsic liver disease. If dramatic elevations of ALT take place (i.e., >3X baseline or >5X ULN), my advice would be to watch the trend and consider holding all drugs possible while the liver tests subside. If from the myriad possibilities, the clinician determines the statin may be the cause, the statin can be switched. In the current study by Bjornsson *et al.*, when patients were switched, the subsequent statin did not elicit an idiosyncratic reaction.

In summary, the elevation of ALT values that commonly occur at the start of statin therapy have no meaning in regard to hepatotoxicity. On the other hand, Bjornsson *et al.* present data that show drug idiosyncrasy due to statins probably exists, but is rare. ALT monitoring does not help to discover an idiosyncratic reaction. Patients started on statins should be counseled about possible symptoms of drug-induced hepatitis but told how rare this is.

Giving a statin to those patients with liver disease and cardiac risk factors may increase their lifespan more than any other therapy we offer. Writing this prescription would produce greater longevity, with far less risk, than liver transplantation for patients with fatty liver or peginterferon based triple therapy for hepatitis C. For liver patients with cardiac risk factors, the pen is mightier than the knife or needle!

### Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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