Drug Safety 2007; 30 (1): 1-4
0114-5916/07/0001-0001/$44.95/0

Statins and Monitoring of Liver Function Tests

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The HMG-CoA reductase inhibitors, or 'statins', have been studied in numerous controlled human research trials involving hundreds of thousands of study participants and have been prescribed for millions of patients. These drugs have been shown to improve lipid blood levels and reduce the risk of atherosclerotic coronary artery disease (CAD), resulting in reduced CAD morbidity and mortality, and in several studies they have reduced overall all-cause mortality.

In recent years, many patients and health professionals have questioned the safety of statins. There have been indications from the media and from clinical experience that some patients refuse to initiate statin therapy while others choose to withdraw from long-term statin treatment because of concerns about safety.[1] These concerns have arisen from information obtained from the news media, direct-to-consumer advertising and the Internet. Health professionals are also expressing concerns, perhaps out of a response to their patients' sentiments but also because of the withdrawal of cerivastatin from the market as a result of serious adverse events, publications reporting statin-related adverse effects and the constant threat of litigation from malpractice lawyers.[2]

The initiation and continuation of statin therapy involves a number of safety obligations, including the assessment and subsequent monitoring of liver function tests (LFTs). However, a recent American National Lipid Association (NLA) Task Force formed to evaluate the value and cost effectiveness of routine LFT monitoring in patients receiving statin therapy has raised serious doubts about whether such monitoring is desirable or of value.

This editorial summarises the available literature regarding statins and liver toxicity and examines the question of whether LFTs should be routinely monitored with statin therapy.

1. Summary of the Liver Task Force's Findings and Recommendations

The NLA appointed a Safety Assessment Task Force to address concerns about the safety of lipid-modifying therapies and evaluate the usefulness of routine LFT monitoring. The Task Force presented their findings regarding statin safety at a meeting convened from 17 to 19 July 2005, at the Mandarin Hotel in Washington, DC, USA. The report from this meeting was published in the *American Journal of Cardiology*.[3]

The NLA Task Force concluded that there was neither any evidence that a relationship existed between elevated serum aminotransferase levels, statin therapy and the subsequent risk of developing significant liver injury, nor that routine monitoring of LFTs identified individuals likely to develop rare cases of idiosyncratic liver failure. Therefore, they recommended that the requirement for routine LFT monitoring in patients receiving any of the currently marketed statin therapies should be re-examined.[4-6] The Task Force was concerned that isolated elevations in aminotransferases may prompt health professionals to discontinue statin therapy inappropriately in patients otherwise at increased risk for an adverse cardiovascular outcome. This is of particu-

lar concern as there is a high prevalence of LFT abnormalities in patients with hypercholesterolaemia and/or patients with type 2 diabetes mellitus in whom hepatic steatosis is prevalent. The Panel was also concerned that patients may be unduly alarmed by the perceived implications of monitoring and may choose to discontinue or refuse statin therapy. Finally, preliminary estimates suggest that the costs associated with LFT monitoring are very high.

Before instituting any type of medical therapy, it is advisable for the clinician to perform a complete and systematic history, physical examination and relevant laboratory testing. If, in the course of this workup, elevated aminotransferase levels are identified, they should be investigated in an appropriate fashion. Hyperlipidaemic patients with chronically abnormal liver biochemical tests should undergo appropriate investigations to determine the cause, particularly to detect the presence of hepatic steatosis or cholelithiasis, and, if indicated, be referred to a gastroenterologist for further management. However, there is no evidence that the presence of elevated LFTs due to these causes represents either a contraindication to statin therapy or a predictor of the risk of severe hepatotoxicity. In contrast, denial of statin therapy in such patients may be deleterious to the patient.

Other than measuring LFTs for the purpose of periodically updating a patient's medical history, the panel could find no scientific or medical basis for monitoring aminotransferase levels during long-term statin therapy as a measure to enhance patient safety.

There is no evidence that statin therapy should be altered or discontinued solely on the basis of elevated LFTs in an asymptomatic patient. Should more objective evidence of hepatic dysfunction be identified, such as hepatomegaly, clinical evidence of jaundice, elevated direct bilirubin levels or increased prothrombin time, statin therapy should be discontinued.[7] The patient should be evaluated appropriately and referred to a gastroenterologist or hepatologist if necessary. However, it should be emphasised that this situation is extremely rare and does not appear to be predicted by prior asymptomatic LFT abnormalities.

Elevated LFTs due to statins do not affect the response to anticoagulant therapy. Therefore, no modification in statin therapy is recommended. Furthermore, mild to moderate alcohol consumption is not a contraindication for statin therapy.[8]

The risk of adding statin therapy to the treatment of patients with significant chronic liver disease (whether due to alcohol or other causes) is uncertain but there is no evidence at this stage that use of statins in these patients further impairs liver function. Nonetheless, current product information warns against the use of statins in patients with aminotransferase levels >3 times the upper limit of normal (ULN). It should be noted that this restriction is a routine and arbitrary one related to standard clinical trial design applied during the development process of the product and does not necessarily reflect experience with the use of these drugs in the community. It would seem logical to balance the uncertain risk of hepatotoxity with the likely cardiovascular benefit of statin therapy in patients with chronic liver disease and a high risk of cardiovascular events.

2. Statin-Induced Hepatotoxicity

Very rare case reports of liver failure have occurred in patients receiving statin therapy.[9,10] Because the association between statin therapy and liver failure is rare, it has not been possible to directly attribute liver failure to statin usage. Nevertheless, it is possible that these cases do represent an idiosyncratic reaction to a statin.

When there is concern about the possible occurrence of a hepatotoxic reaction due to statin therapy (e.g. if the patient reports jaundice, malaise, fatigue, lethargy or related symptoms during treatment), an assessment of the fractionated bilirubin level is of value. In the absence of biliary obstruction, bilirubin is a more reliable prognostic predictor of liver injury due to drug toxicity.[11] If the direct fraction of bilirubin is found to be increased in association with elevated aminotransferase levels, it is reasonable to assume that there is ongoing liver injury and further

appropriate testing should be undertaken to ascertain the aetiology. However, significant liver damage appears to be extremely uncommon with statins, especially when one considers the magnitude of their use worldwide. Based on 232 cases of acute liver injury potentially associated with lovastatin that were reported to Merck's Worldwide Adverse Event Database, it was estimated that risk of liver failure attributable to lovastatin was 2 per 1 million patients.[12] Law and Rudnicka[13] estimate that the incidence of statin-associated liver failure is about 1 per 1 million person-years of use. Of the 51 741 patients who underwent liver transplantation in the US between 1990 and 2002, there were three patients in whom the procedure was performed for acute liver failure thought to be caused by statins.[9] Of these three patients, two had acute liver failure while receiving cerivastatin and one had liver failure that was apparently associated with simvastatin. After an extensive review of the literature, the Task Force could find no direct evidence of death due to liver failure caused by statin therapy.

3. Mechanism of Statin-Induced Hepatotoxicity

The mechanism that underlies the rare association of acute liver failure and statin therapy is not clear. Statins have been reported to unmask autoimmune-type liver pathology in genetically predisposed individuals, but this appears to be very rare.[14] Furthermore, the rare occurrence of liver failure due to an idiosyncratic reaction is not specific to statins and has been reported with a number of other commonly used medications (e.g. isoniazid, nitrofurantoin).[7]

4. Reversibility of Statin-Induced Liver Function Test (LFT) Elevations

Charles et al.[15] evaluated data from a large health maintenance organisation on 23 000 patients who were treated with statins and who had had ALT level tests performed. A total of 62 (0.3%) individuals were found to have ALT levels >10 times the ULN. Elevated ALT levels were thought to be caused by statin treatment in 17 of these 62 patients. Thirteen of these 17 cases were thought to be associated with potential drug interactions. Of the four cases that did not appear to be potentially associated with drug interactions, three involved patients with heart disease, diabetes or both; the remaining patient was of a 71-year-old woman treated with atorvastatin 80 mg/day. In 16 of the 17 patients with statin-associated marked elevations in ALT, the transaminase levels resolved upon discontinuation of statin therapy; the remaining case was an 80-year-old woman with severe heart failure who died of her heart failure shortly after statin therapy was commenced. It is likely that hepatic congestion due to severe heart failure was the predominant cause of her elevated liver function tests.

In the vast majority of cases, any suspected statin-related marked elevations in ALT levels that occur resolve upon discontinuation of statin therapy. However, the incidence of these marked elevations is extremely uncommon and their significance is uncertain.

5. Dose Response and Differences between Statins in the Elevation of LFTs

The risk of asymptomatic elevations in LFTs appears to be dose dependent for most statins.[16-18] There is little information available concerning differences between the risk of LFT elevations between equivalent cholesterol-lowering doses of different statins. In the long-term morbidity and mortality trials pravastatin the incidence of LFT abnormalities was no greater than placebo.[19] Pravastatin was studied at a single dose of 40 mg/day in these trials and the degree of low-density lipoprotein-cholesterol reduction achieved was substantially less than that achieved by higher doses of atorvastatin.

6. Conclusions

For the vast majority of patients who require statin therapy, there is evidence that these drugs are both effective and safe. There is a valid concern that the inappropriate exclusion of patients from statin therapy because of common causes of LFT abnormalities such as hepatic steatosis or the development of mild LFT elevations during statin therapy may

result in the an avoidable increase in cardiovascular morbidity and mortality. There is considerable merit in the recommendations proposed by the Safety Task Force of the NLA to forego routine monitoring of LFTs in patients receiving statin therapy. Nonetheless, for medicolegal reasons, the product labeling of these drugs must be adhered to at the present time. This states that LFTs should be assessed prior to initiation of therapy and periodically thereafter. If elevated LFTs occur that are <3 times the ULN, they should continue to be monitored. If elevation of LFTs to >3 times the ULN occur, it is recommended that the dose of the statin be reduced and LFT monitoring continued. This is in contrast to the frequent practice of stopping therapy altogether.

While the monitoring of LFTs in patients receiving statin therapy remains a necessity at this stage, it is important for medical practitioners to appreciate the significance, or lack thereof, of LFT abnormalities in patients for whom statins are indicated. They also need to have an appropriately high regard for the value of continuing these lifesaving drugs in patients for whom they have been shown to be of proven benefit.

Acknowledgements

No sources of funding were used in the preparation of this editorial. Both authors are involved with an ongoing trial involving atorvastatin and both authors have from time to time received honoraria for presentation or advisory boards sponsored by the manufacturers of statins.

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