REVIEW

CME CREDIT

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How to use statins in patients with chronic liver disease

ABSTRACT

Clinicians may be concerned about prescribing statins to patients with chronic liver disease, but there is little evidence to suggest that drug-induced liver injury from statins is increased in these patients. Thus, we should prescribe statins for the same indications in patients with chronic liver disease as in patients without, but with closer monitoring. However, patients with acute liver disease (acute viral hepatitis, alcoholic hepatitis) should not take statins until they have recovered.

KEY POINTS

Hepatotoxicity from statins typically leads to an elevation in aminotransferase levels, reflecting hepatocellular injury as opposed to cholestatic injury.

The benefits of statins in lowering cholesterol and preventing heart disease outweigh the potential risks of hepatotoxicity, even in patients with chronic liver disease.

Liver enzymes should be monitored in all patients who take statins. If the alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level doubles, the statin should be stopped.

Elevation in liver enzymes with statin therapy is dose-related. We recommend starting statin therapy at low doses in patients with chronic liver disease and checking liver enzymes after any increase in dose.

WHEN A PATIENT NEEDS a statin to prevent or treat coronary artery disease, we should prescribe one—even if he or she has chronic liver disease or a history of acute liver disease.

Even though there are no large studies of statin use in chronic liver disease, and drug labels caution physicians about using statins in patients with liver disease, statin-induced liver injury is uncommon, and there is little evidence so far to suggest that it is any more likely to occur in patients with chronic liver disease than in those without it.

Thus, statins can and should be prescribed for the same indications in people with chronic liver disease as they are in people without chronic liver disease—provided we closely monitor aminotransferase levels for signs of liver toxicity or muscle damage.

Patients with active acute liver disease such as acute viral hepatitis or alcoholic hepatitis should not receive statins until they have recovered.

In this article we review the data on statin-induced hepatotoxicity and offer our recommendations on the use of statins in patients with chronic liver disease, which are based on data from patients without liver disease and on our own clinical experience.

TYPES OF DRUG-INDUCED LIVER TOXICITY

Drug-induced liver injury is uncommon, but in rare circumstances it may lead to liver failure. It is typically classified as either hepatocellular or cholestatic. Elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) indicate liver cell damage, whereas elevations in total bilirubin, alkaline phos-

TABLE 1

Rates of aminotransferase elevation and drug discontinuation for various statins

STATIN	REFERENCE	PATIENTS	INCIDENCE OF ELEVATION IN AST OR ALT* LEVEL >2 OR 3 TIMES UPPER LIMIT OF NORMAL	DISCONTINUATION
Atorvastatin (Lipitor)	2,4	1,072	0–0.7%	N/A
Cerivastatin (Baycol)	1,2	1,263	0–0.5%	N/A
Fluvastatin (Lescol)	3	822	1.2%	0.6%
Lovastatin (Mevacor)	1,5	3,304	0.6%	0.2%
Pravastatin (Pravachol)	6,7	5,170	1.3%	0.1%
Rosuvastatin (Crestor)	11	1,123	0%	0%
Simvastatin (Zocor)	8	10,269	1.8%	0.5%

*AST = aspartate aminotransferase; ALT = alanine aminotransferase

phatase, and gamma-glutamyl transferase (GGT) reflect cholestasis. Injury from statins is hepatocellular and is therefore indicated by elevations in AST and ALT levels. These elevations are usually asymptomatic and transient and resolve after discontinuation of the drug.

In general, continued exposure to hepatotoxins seems to result in greater injury. Therefore, although some classes of drugs are associated with idiosyncratic reactions, early recognition of drug-induced liver injury is critical to ensure that the offending drug is stopped as soon as possible.

METABOLISM OF STATINS

The statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) undergo first-pass hepatic metabolism. Although most statins are metabolized via the cytochrome P450 system, they may utilize a different isoenzyme, which may change their properties. It is important to monitor levels of other drugs the patient may be taking that are metabolized by the same isoenzyme (eg, phenytoin).

Patients with advanced cirrhosis have 10-fold to 20-fold increases in levels of statins as measured by the area under the curve.[1] However, patients with cirrhosis typically have low cholesterol levels and do not require cholesterol-lowering agents.

Incidence of aminotransferase abnormalities in statin trials

As a class, statins have been tested in more than 20,000 people. In clinical trials evaluating statins, which excluded patients with liver disease, the protocols called for stopping therapy if there was a threefold elevation above the upper limit of normal of AST or ALT on two occasions.[2–8] The trials reported no elevation of total bilirubin or jaundice in patients with aminotransferase elevations. The rates of aminotransferase elevation and drug discontinuation for the various statins are shown in TABLE 1.

Statins can and should be used, if needed, despite chronic liver disease

Atorvastatin (Lipitor) was studied in 1,072 subjects, and elevations in aminotransferases were seen within the first 12 weeks of therapy.[4] The elevations were dose-related, with a rate of 0.2% with 10 mg vs 2.3% with 80 mg. Atorvastatin undergoes first-pass hepatic metabolism but is not cycled through the enterohepatic circulation. Increased drug levels are seen in patients with advanced cirrhosis.

Cerivastatin (Baycol) was studied in a trial of 1,263 subjects, and the investigators reported a low incidence of AST or ALT elevation.[2] Aminotransferase elevations were dose-related. After stopping the drug, the enzyme levels returned to normal, although the time needed for these levels to return to normal was not

reported. Cerivastatin was removed from the market because of a higher than expected incidence of death when used in combination with other lipid-lowering drugs.[9]

Fluvastatin. Trials of fluvastatin (Lescol) reported that most aminotransferase elevations occurred within 12 weeks of starting therapy.[3] All patients with persistent AST or ALT elevations had abnormal levels at baseline and at 8 weeks after starting therapy. The incidence of enzyme elevation was dose-related, with a rate of 0.2% in patients receiving 20 mg vs 2.7% in those receiving 80 mg.

Lovastatin. Elevations in aminotransferase levels due to lovastatin (Mevacor) appear to be uncommon. Studies showed that 1.9% of patients receiving the drug had elevations in AST or ALT three or more times the upper limit of normal.[5,10] As with other statins, elevations in aminotransferases were dose-related, with elevations seen in 0.1% of patients treated with 20 mg vs 1.5% of patients treated with 80 mg. Only 0.2% of patients stopped therapy because of aminotransferase elevations. In patients followed for a median of 5 years, 0.6% of those taking lovastatin and 0.3% of those taking placebo had a threefold or greater elevation in AST or ALT levels.

Amino-transferase elevations usually occur in the first 12 weeks of statin therapy

Pravastatin (Pravachol) undergoes first-pass hepatic metabolism, and serum levels are increased about 18-fold in cirrhotic patients. In clinical trials, the rate of aminotransferase elevation was 1.3% in patients treated for 18 months.[6,7] One in 1,000 in the treatment group and 0.03% of the placebo group stopped therapy due to a threefold or greater elevation in AST or ALT.

Rosuvastatin (Crestor) has been approved to treat hyperlipidemias, and in large clinical trials it has not been associated with elevations in ALT or AST that required dose reduction or discontinuation.[11,12] In a trial of 1,123 patients treated with 10 mg to 80 mg of rosuvastatin, no patients were reported to have required dose reduction or discontinuation of rosuvastatin due to aminotransferase elevations.[11]

The pharmacodynamics of rosuvastatin were studied in six patients with cirrhosis.[13] Those with the most advanced liver disease had the highest area under the curve. Rosuvastatin was well tolerated in all patients, and the LDL reductions seen were similar to those seen in patients with normal hepatic function.

Simvastatin. One percent of those treated with simvastatin (Zocor) developed elevations in AST or ALT.[8] Therapy was stopped due to aminotransferase elevation in 0.3% of the treatment group and 0.2% of the placebo group. Elevations of AST or ALT were more common with the 80-mg dose than with the 40-mg dose (2.1% and 0.9%, respectively).

Consistent themes in statin trials

Several themes are consistently seen in the statin trials.

- Hepatotoxicity is rare (rates below 2%), but when it does occur, it manifests as an elevation of AST or ALT
- Elevations of AST or ALT are asymptomatic; jaundice or hyperbilirubinemia are rarely associated with statins
- Hepatotoxicity is dose-related, with higher statin doses associated with a higher rate of liver enzyme abnormalities
- Elevations of aminotransferase levels usually occur within the first 12 weeks of therapy
- AST and ALT levels return to normal with discontinuation of therapy.

WHY WE SHOULD USE STATINS IN PATIENTS WITH CHRONIC LIVER DISEASE

Patients with acute liver disease (eg, acute viral hepatitis A or B, alcoholic liver disease) should not take statins until they have recovered from the acute insult and until levels of AST, ALT, total bilirubin, and alkaline phosphatase have returned to normal. The potential risks of exacerbating liver injury do not justify adding statins during the recovery period.

Chronic liver disease is common: an estimated 1.8% of the US population is infected with hepatitis C, and up to 20% of the population has elevated liver enzymes from nonalcoholic fatty liver disease or other causes.[14] Thus, it is inevitable that clinicians will encounter the issue of statin therapy in patients with chronic liver disease. We believe patients with chronic liver disease with indications for statin therapy should be treated.

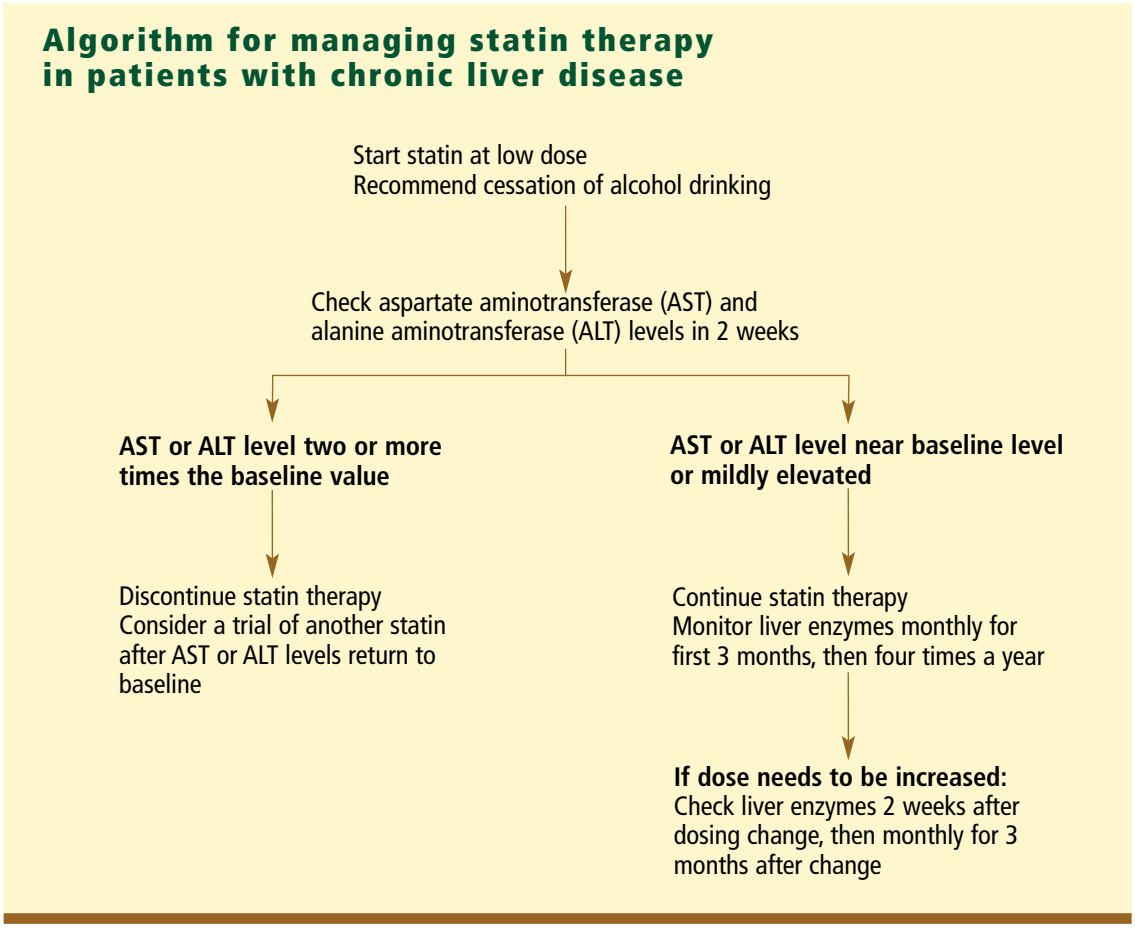

FIGURE 1

Why we think they are safe in these patients

Unfortunately, clinical trials of statin therapy have excluded patients with a history of chronic liver disease or cirrhosis, so current data on statin use in patients with chronic liver disease are limited to case reports or small trials.

Statins and fibrate drugs rarely cause fibrosis and active hepatitis.[15] An analysis of 24 million patient-years of clinical experience with lovastatin reported that the rate of acute liver failure with lovastatin is approximately the same as the background rate of idiopathic acute liver failure, or 1 per 1.14 million patient-treatment years.[10]

Statins are used after liver transplantation to treat hyperlipidemia. In a randomized trial of 16 liver recipients with hyperlipidemia, pravastatin and cerivastatin effectively lowered cholesterol levels.[16] There were no elevations in liver enzymes attributed to statin therapy and no need for dose reduction or discontinuation.

Long-term safety. The data are even sparser on the long-term safety of statins in patients with liver disease.[17] Most of the clinical trials of statins in patients without liver disease were less than 2 years in duration. However, most elevations in aminotransferase levels occur during the first 12 weeks of therapy. Thus, acute liver injury seems to occur soon after the drug is started.

Whether long-term statin use increases or decreases liver fibrosis is unknown. Two patients who underwent liver biopsy after developing elevations in aminotransferase levels after lovastatin and simvastatin were found to have liver fibrosis.[15] However, these patients did not undergo pretreatment liver biopsy, and they had risk factors for nonalcoholic fatty liver disease. Thus, the liver fibrosis seen in their biopsy specimens

Chronic liver disease is common, so clinicians will inevitably face the issue of whether to give statins

may have been a result of nonalcoholic steatohepatitis.

OUR RECOMMENDATIONS

If patients with chronic liver disease have an indication for statin therapy, then a statin should be prescribed. The small body of existing literature and our clinical experience suggest that hepatotoxicity from statin therapy is not increased in patients with chronic liver disease.[17]

We are particularly cautious in patients with aminotransferase levels that are three or more times the upper limit of normal. In these patients, we investigate the cause of liver disease before prescribing a statin.

However, given that there are so few data in this area, and given that additional research on this topic is sorely needed, we monitor liver enzymes more closely in patients with chronic liver disease.

Because data from clinical trials demonstrate that hepatotoxicity is dose-related, we recommend starting statin therapy at low doses in patients with chronic liver disease.

In addition, since most aminotransferase elevations are seen within the first 12 weeks of starting therapy, we suggest more frequent monitoring during the first 3 months of therapy. We recommend stopping statin therapy if AST or ALT levels rise to two or more times the baseline level; after AST or ALT levels return to normal, we consider a trial of another statin.

Again, these recommendations are not based on direct evidence from patients with chronic liver disease, but instead from data on patients without liver disease and from our clinical experience. **FIGURE 1** provides a general guideline of the frequency in which we monitor liver enzymes, also based on indirect evidence and on our own clinical experience.

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