ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Use of Statins in Patients With Cirrhosis

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G&H Traditionally, what have been the main concerns with the use of statins in patients with cirrhosis?

DK Among primary care providers, there has frequently been a concern regarding the potential hepatotoxicity of statins, and various statin use guidelines continue to warn of this risk. However, the rate of true statin-induced hepatotoxicity is exceedingly low. Moreover, multiple retrospective studies have shown that statins are not only safe for use in patients with cirrhosis, but are also likely beneficial in reducing liver decompensation, hepatocellular carcinoma, infections, and death.

What confounds the concern related to statin-induced hepatotoxicity is that a very high percentage of patients for whom statins would likely be prescribed (eg, patients with cardiovascular risk factors such as diabetes, high blood pressure, coronary artery disease, and dyslipidemia) have fatty liver and/or nonalcoholic steatohepatitis. Therefore, many of the abnormal liver enzyme test results attributed in the past to the use of statins were more likely caused by the underlying fatty liver/nonalcoholic steatohepatitis than the drugs themselves. Interestingly, it is these same patients with fatty liver who gain the greatest cardiovascular benefit from the use of statins.

G&H What types of effects can statins have in patients with cirrhosis?

DK Statins have multiple beneficial properties independent of their cholesterol-lowering effect. Human studies have shown that statins have a modest direct effect in lowering portal vein blood pressure due to vasodilatory properties. Statins also have anti-inflammatory properties. There is other evidence that statins affect vascular reactivity and remodeling, which may be beneficial in some of the vascular changes in the liver that occur with progressive fibrosis. There are also increasing amounts of in vitro, small animal model, and human clinical data suggesting that statins have anti-inflammatory and antifibrotic properties in multiple tissues such as the lungs, kidney, and heart. More recent and increasingly convincing data show that statins alter the development of cirrhosis by reducing progression from precirrhotic chronic liver disease to cirrhosis, which decreases the risks of decompensation, hepatocellular carcinoma, and death.

G&H Have these effects been seen in all patients with cirrhosis or only in certain subgroups?

DK Several large retrospective studies generated from populations of cirrhosis predominantly related to chronic hepatitis B virus, chronic hepatitis C virus, and alcoholic liver disease have found associations between statins and reduced morbidity and mortality. These studies include large population-based studies, one on chronic hepatitis B virus infection from Taiwan and one on chronic hepatitis C virus infection from the US Veterans Affairs (VA) system. Both of these studies showed a strong association between statin exposure and improvement in hepatic decompensation, cancer, and death. To date, there has only been 1 prospective, randomized, controlled trial of statins, conducted by Abraldes and colleagues in Spain,

which enrolled patients with Child-Pugh A or B of diverse etiologies who were given statins in addition to standard-of-care banding and nonselective β-blockers to determine whether the treatment would reduce rebleeding rates associated with an initial variceal hemorrhage. The study did not meet its primary endpoint in that there was no difference in rebleeding between the 2 arms, but there was a marked survival benefit for the patients who received statins independent of the underlying disease etiology.

My colleagues and I have a paper currently under review in which we retrospectively looked at the national VA data of all patients with cirrhosis of all etiologies. Looking at different disease subgroups, we found that the magnitude of the beneficial effect of statins was slightly stronger in patients who had fatty liver disease or alcoholic liver disease than patients with viral hepatitis. However, we identified significant benefits in all disease subgroups of patients with compensated cirrhosis.

G&H Could you further discuss how liver disease severity might impact the effect of statins on survival in patients with cirrhosis?

DK Existing data suggest that some cirrhotic patients are too sick to benefit from statins and/or are at higher risk for statin-related complications. In the aforementioned study by Abraldes and colleagues, the enrolled patients were all decompensated with variceal hemorrhage and, by definition, had clinically significant portal hypertension. Statins were found to confer a survival benefit. Although this study clearly needs to be externally validated, the impact was dramatic. However, among Child-Pugh B patients, the authors observed a relatively high rate of rhabdomyolysis (3 patients in the arm receiving simvastatin 40 mg daily developed rhabdomyolysis). All 3 of these individuals had total bilirubin levels greater than 3 mg/dL. Thus, this study provides a possible threshold of total bilirubin above which statins might be considered excessively risky.

When my colleagues and I retrospectively looked at the VA cohort of patients with cirrhosis, we found a significant trend toward an increased decompensation rate in Child-Pugh B and C patients who received statins, suggesting again that patients with very advanced cirrhosis may experience more harm than benefit associated with initiating or continuing statin therapy. Thus, most of the survival benefit appears to be associated with Child-Pugh A patients with or without clinically significant portal hypertension but without other manifestations of liver failure.

G&H Are there any limitations to these study data?

DK One of the drawbacks of retrospective studies that look at the association of statins and survival is that there is a very strong selection bias associated with the receipt of statins among patients with cirrhosis (also known as confounding by indication). The patients with cirrhosis whose livers are well enough to make cholesterol are more likely to be treated with statins. In addition, the hypercholesterolemia phenotype is strongly associated with well-compensated liver disease. Thus, cirrhotic patients who are selected to receive statins tend to be the patients who have Child-Pugh A cirrhosis, higher albumin levels, higher platelet levels, lower international normalized ratios, lower bilirubin levels, and no liver complications. Therefore, it is still not completely clear from retrospective studies that the survival benefit associated with statin exposure is due to the pharmacologic effects of the statin or the effects of being a candidate who is prescribed a statin. It is critical for the hepatology field to address this issue with prospective, randomized, controlled trials, as it is not possible to fully control for confounding by indication in retrospective studies.

G&H According to the research conducted to date, do statins offer any other benefits or risks in patients with cirrhosis?

DK There are currently no clear prospective or retrospective data that statins improve cardiovascular or other nonhepatic outcomes in patients with cirrhosis. However, there is obviously a large literature showing cardiovascular benefits of statins in noncirrhotic patients. It is likely that the competing risk of hepatic morbidity and mortality might make it methodologically challenging to confirm cardiovascular benefits in cirrhotic patients. Bajaj and colleagues at Virginia Commonwealth University looked retrospectively at patients with cirrhosis who were exposed to statins, and found a reduction in the rate of infections. This effect was probably mediated through lower rates of liver decompensation rather than a direct antimicrobial effect. Thus, the available data suggest that the primary benefits of statin use are reducing liver disease progression, lowering portal hypertension, and retarding carcinogenesis.

G&H Has any research compared different statin formulations in patients with cirrhosis?

DK There are not adequate data to compare one statin formulation to another at present. The only prospective, randomized, controlled studies have used simvastatin 40 mg daily. In the larger VA cohort, my colleagues and I did not see any significant difference between commonly used statins such as simvastatin and atorvastatin.

However, there are several theoretical reasons that one statin formulation might be preferred over another. One is that the risk of rhabdomyolysis appears to be associated with specific genetic polymorphisms that impact the metabolism of some statins but not others. For this reason, atorvastatin might be safer than simvastatin. Also, atorvastatin is a nitric oxide donor, so it might have a slightly different impact on vascular reactivity. At this point, however, these are all theoretical advantages not supported by any clinical data.

G&H Based on the research conducted to date, should doctors prescribe statins to all patients with cirrhosis who have an indication for statins?

DK We have strong data that patients who have an indication for a statin due to cardiovascular risk factors such as diabetes, preexisting coronary artery disease, cerebrovascular disease, or peripheral arterial disease definitely should be prescribed statins. We do not have sufficient evidence yet to prescribe statins universally in patients with cirrhosis independent of a standard indication for statins. However, if data from the study by Abraldes and colleagues are confirmed in other centers, we may be closer to being able to recommend statins to all patients with cirrhosis.

G&H Are there any contraindications to the use of statins in cirrhotic patients?

DK Contraindications for statin use include previous sensitivity to a statin and prior true statin-induced hepatotoxicity. In addition, data from my colleagues and I as well as from other groups suggest that Child-Pugh B and C patients probably should not be prescribed statins.

G&H What is the ideal dose and duration of statins in cirrhotic patients?

DK We do not have any specific data in terms of the ideal dose or duration. Data from my colleagues and I suggest that in patients with Child-Pugh A cirrhosis, every year of statin exposure is associated with an approximately 15% relative risk reduction of death, and that the longer the patients are exposed, the more benefit there is. However, prospective, randomized, controlled trials are needed to address questions of dose and duration.

G&H How should cirrhotic patients on statins be monitored?

DK The US Food and Drug Administration recommends 1-time liver testing soon after initiating or changing a statin but has dropped any recommendations for routine liver panel monitoring in noncirrhotic patients prescribed statins. I recommend that doctors be a little more cautious with statins in cirrhotic patients and monitor liver-associated enzymes in the first month of statin use and then perhaps every 3 to 6 months thereafter. However, that monitoring recommendation may be too conservative because for the vast majority of patients, these medications are quite safe for long-term use. If a patient with Child-Pugh B or C cirrhosis comes to my office already on a statin, particularly with a total bilirubin level greater than 3 mg/dL, I would be inclined to stop the statin. If the patient or other involved clinicians insist on continuing the statin, it is important to be cognizant of any new muscle-related symptoms that could be signs of early myopathy or rhabdomyolysis.

G&H What are the most important next steps in research in this area?

DK Prospective, randomized, controlled trials are needed to validate the study by Abraldes and colleagues, which found a survival benefit with the use of statins in patients with clinically significant portal hypertension and variceal hemorrhage. Thereafter, the study populations should be broadened to examine the effect of statins on decompensation, cancer, and death in patients with Child-Pugh A cirrhosis who have not had variceal hemorrhage but are likely to have clinically significant portal hypertension. Ultimately, if statins are shown to have consistent benefits in sicker compensated cirrhotic patients, then randomized, controlled trials will be needed in a general cirrhosis population to confirm survival benefits.

Dr Kaplan has no relevant conflicts of interest to disclose.

Suggested Reading

Abraldes JG, Villanueva C, Aracil C, et al; BLEPS Study Group. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. *Gastroenterology.* 2016;150(5):1160-1170.e3.

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