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Statins and Liver Disease: Is it Time to Recommend Statins to Prevent Liver Disease Progression?

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Abstract

Evidence is emerging that statins may reduce liver-related adverse outcomes in individuals with chronic liver disease. In this issue of the *American Journal of Gastroenterology*, Kamal *et al.* found in their meta-analysis that statin use was associated with a reduced risk of fibrosis progression, decompensated cirrhosis, and mortality. These encouraging findings suggest beneficial liver effects of statins. However, the overall quality of the evidence is low because 9 of the 10 studies included in the meta-analysis were observational. More robust studies, including randomized trials and research on safety in patients with advanced liver disease, are needed before statins can be routinely recommended for prevention of liver-related morbidity and mortality.

Statins are among the most widely prescribed drugs and have well-established cardiovascular benefits (1). However, providers have been reluctant to prescribe statins in patients with chronic liver disease because they can cause asymptomatic elevations in serum aminotransferases as well as severe liver toxicity, although the latter is very rare (2). The National Lipid Association's Safety Task Force convened a Liver Expert Panel to address these concerns; the group concluded that statins should be prescribed when clinically indicated in patients with chronic liver disease except in those with decompensated cirrhosis (3). These recommendations have recently been reaffirmed by the panel after review of the interval data showed no new unexpected hepatic safety issues (4).

More recently, the focus has shifted from whether statins are harmful in patients with chronic liver disease to whether they may be helpful in preventing liver-related morbidity and mortality. A retrospective cohort study of over 90,000 patients with pre-existing liver disease in a large integrated health plan aimed to assess the risk of liver toxicity associated with lovastatin exposure and found that the medication was associated with a lower incidence of liver injury, cirrhosis, and liver failure (5). Multiple subsequent cohort analyses have similarly observed an association of statins with fewer adverse liver outcomes,

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CONFLICT OF INTEREST

Potential competing interests: Jennifer C. Price discloses grant support from Gilead Sciences and Merck and ownership interest in Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie. Phyllis C. Tien has no conflicts to disclose.

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including a decreased risk of hepatocellular carcinoma (6). This has led many to consider whether statins' pleiotropic effects extend beyond cardiovascular disease and are beneficial to the liver as well.

In this issue of the *American Journal of Gastroenterology*, Kamal *et al.* (7) present a systematic review and meta-analysis evaluating the impact of statins on fibrosis progression, development of hepatic decompensation, and mortality in individuals with chronic liver disease. Ten studies were included; nine studies were observational and one was a randomized control trial. Five studies were restricted to patients with hepatitis C virus (HCV), including one in HIV–HCV-coinfected patients, two were in patients with hepatitis B virus, and three included patients with any cause of liver disease. Among the six studies that assessed the primary outcome of fibrosis progression and development of cirrhosis, statin use was associated with a pooled hazard ratio (HR) of 0.49 (95% confidence interval (CI) 0.39–0.62). The authors similarly found that statins were associated with a decreased risk of the secondary outcomes of decompensated cirrhosis (three studies; HR: 0.54, 95% CI: 0.46–0.65) and mortality (four studies; HR: 0.63, 95% CI: 0.44–0.90). However, because almost all of the studies included in the meta-analysis were observational, the overall quality of the evidence is low.

Selection or channeling bias is a concern when relying on data from observational studies, because statins are prescribed at the discretion of the provider and the indication for prescribing or not prescribing statins is not known. Only one study in the meta-analysis was a randomized controlled trial, which is less prone to bias. It is well documented that statins are underutilized in patients with liver disease, and a survey of primary care physicians indicated that this is in large part due to ongoing concerns about hepatotoxicity (8). It is possible that patients who were not prescribed statins had worse liver dysfunction or were otherwise more sick than those prescribed statins. The observational studies included in the meta-analysis did adjust for comorbidities, and some used propensity scores to address potential confounding by indication. Nevertheless, residual confounding remains a large concern. This is an inherent limitation of the observational design and is why the quality of the evidence was deemed low.

Another limitation that is often inherent to systematic reviews and meta-analyses, especially related to liver disease, is the heterogeneity both in the methods used by the individual studies to estimate fibrosis progression and the underlying patient populations. The authors addressed this thoroughly—they performed a subgroup analyses based on the method of defining fibrosis progression, a subgroup analysis based on study quality, and a sensitivity analysis limited to the studies in HCV-infected patients. The results of all of these analyses remained in favor of a potential protective effect of statins. Additional limitations to the study include a lack of granularity regarding specific statin use and dose and absence of information on adverse side effects of statins.

There are several potential mechanisms by which statins may exert protective effects on the liver (9). Statins inhibit hepatic stellate cell activation and cytokine production, leading to decreased hepatic fibrogenesis and reduced portal pressure. Statin-induced increases in hepatic endothelial nitric oxide synthase also contribute to portal pressure

reductions. Indeed, in a randomized controlled trial of 59 patients with cirrhosis and clinically significant portal hypertension, hepatic venous pressure gradient was decreased with simvastatin (10). In addition, statins appear to have chemopreventive effects, including inducing apoptosis and inhibiting angiogenesis in hepatocellular carcinoma. Finally, statins directly inhibit HCV viral replication and may lead to improvements in hepatic steatosis.

However, statins are not without harm, and the risks in patients with decompensated cirrhosis are largely unknown. In particular, statin-related myopathy is one of the most clinically important complications of statins and the risk increases with higher drug doses. Advanced liver disease is a potential risk factor for statin-induced myopathy, presumably due to higher serum drug concentrations in the setting of impaired hepatic metabolism. Other risk factors for statin-induced myopathy include renal insufficiency, frailty, advanced age, and drug–drug interactions, all of which are common in patients with advanced cirrhosis (11). The most severe and potentially life-threatening manifestation of statin-induced myopathy is rhabdomyolysis. Fortunately rhabdomyolysis is rare, with reported rates from the US Food and Drug Administration Adverse Event Reporting System ranging from 0.3 cases to 13.54 cases per 1 million prescriptions (11). Notably, however, in the one randomized controlled trial included in the meta-analysis by Kamal *et al.*, 2 out of 69 patients in the simvastatin group (2.8%) and none in the placebo group experienced rhabdomyolysis. Both of the patients with rhabdomyolysis had normal baseline renal function but significantly impaired liver synthetic function with bilirubin >5; both recovered completely after cessation of the statin (12). Others have described statin-induced rhabdomyolysis in a patient with decompensated cirrhosis awaiting liver transplantation (13). At our own institution, we have seen three cases of severe rhabdomyolysis (two fatal) in patients with decompensated cirrhosis who were taking a statin and were undergoing evaluation for liver transplant.

Is it time to consider endorsing statins in patients with liver disease to prevent liver-related morbidity and mortality? There is now mounting observational evidence of a beneficial effect, a limited number of randomized controlled trials demonstrating benefit, and laboratory studies supporting biologic plausibility of hepatic protection. However, there remain many unknowns, including the optimal statin to select and dosing, particularly in patients with impaired liver function, and the risk of severe non-hepatic adverse events, such as rhabdomyolysis. The study by Kamal *et al.* is encouraging and supports the need for well-designed clinical trials to assess the benefits and safety of statins in this population.

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