



The use of statins in the management of chronic liver disease

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Cirrhosis-related complications are a major cause of morbidity and mortality in patients with liver disease. Once decompensated cirrhosis has established itself, the patients' median survival is less than 2 years (1). It is therefore important to prevent the development of advanced fibrosis, and the ensuing clinically significant portal hypertension (CSPH) (2). At the present time, very few medications have a direct impact on portal hypertension, and beta-blockers are the only ones used regularly in clinical practice. In selective situations, these can achieve an improvement in overall survival and decrease the chance of variceal bleeding. Unfortunately, many patients do not respond to such therapy or only have partial improvement, while others are intolerant to them (3). It is therefore imperative that we identify and implement in clinical practice medications that can slow progression of fibrosis and improve portal hemodynamics after thorough and rigorous efficacy and safety data are made available.

Statins are licensed medication that seems to fit the bill. Initially developed for dyslipidemia, statins have proved to be indispensable in the primary and secondary prevention of cardiovascular events with an improvement in mortality (4,5). Mechanistically, these agents inhibit the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which is the rate limiting step in the biosynthesis of cholesterol (6). In addition to their effect on lipid metabolism, statins have been shown to have beneficial effects on portal hypertension (7). Furthermore, they were identified by the Baveno VI consensus workshop as promising new medications in the management of portal hypertension (8).

The pleiotropic effects of statins have raised a significant degree of interest over the past few years (9). Based on multiple studies in animal models, statins increase endothelial nitric oxide synthase (eNOS) and modulate the contraction of hepatic stellate cells (HSC) (10). This leads to lower intrahepatic resistance and lower portal pressure. Furthermore, statin modulate the activation of HSCs by inducing Kruppel-like factor 2 (KLF2) (11). An overexpressed KLF2 promotes a favorable HSC phenotype and improves liver fibrosis, endothelial dysfunction and portal hypertension (11). Lastly, in a mouse model of sepsis-induced endothelial dysfunction, simvastatin was able to prevent and lessen the degree of endothelial dysfunction by restoring a more physiologic level of eNOS activity (12). Although these studies have been conducted in animal models, they provide biological plausibility supporting the mechanisms behind the beneficial effects of statins in cirrhosis. In a first of its kind human clinical study, Zafra *et al.* showed that simvastatin acutely increased nitric oxide (NO) levels and decreased hepatic resistance (13). This study showed no impact of simvastatin on overall portal pressure as the decrease in hepatic resistance was compensated by an increase in flow. In another study, one month therapy with simvastatin demonstrated that it decreased portal pressure with or without combination with a beta-blocker (14). More recently, a randomized clinical trial from Abraldes *et al.* initiating simvastatin after an episode of esophageal variceal bleeding showed that the addition of simvastatin to standard therapy decreased overall mortality (22% *vs.* 9%, $P=0.03$), but not the rate of rebleeding (15). Unfortunately, this study

included a small number of patients with 78 on placebo and 69 on simvastatin, despite recruiting amongst 14 centers. Regardless, this has sparked a significant amount of interest on the potential benefits of statins in patients with chronic liver disease.

In a recent issue from the American Journal of Gastroenterology, Kamal *et al.* reported the results of their systematic review and meta-analysis assessing the beneficial effects of statins on the rates of hepatic fibrosis, hepatic decompensation, and mortality in patients with chronic liver disease (16). After review of the literature, they identified ten studies which satisfied their inclusion criteria. Nine of the ten studies were retrospective observational studies which conferred a low-quality of evidence to the findings reported based on the GRADE framework (17). The ten studies provided a substantial number of patients for analysis, including 54,441 statin users and 205,012 non-users for comparison. The authors chose the effect of statins on the rate of progression of hepatic fibrosis in patients with chronic liver disease as the primary outcome of interest. For this outcome, the pooled hazard ratio (HR) was 0.49 [95% confidence interval (CI), 0.39–0.62]. Of note, there was significant heterogeneity between studies. This is not surprising given that some studies used FIB4 >3.5, ICD-9 coding, APRI >2, or liver biopsy to define progression of fibrosis or cirrhosis. In order to adjust for this, after grouping the studies based on the method of detection of fibrosis, the pooled HR was 0.58 (95% CI, 0.51–0.65) with no heterogeneity for studies that used ICD-9 coding with a second method. Similarly, on sensitivity analysis focusing on patients with Hepatitis C virus (HCV) infection as the cause of liver disease, the pooled HR for the progression of fibrosis was 0.52 (95% CI, 0.37–0.73). As mentioned above, the quality of this evidence is low as it relied mainly on observational studies.

Regarding the secondary outcome assessing the development of hepatic decompensation, 14,699 patients were available for analysis. Half of the patients were statin users and the rest were non-users (16). Contrary to the varying definition of hepatic fibrosis described above, all three studies which assessed this outcome had the same definition for hepatic decompensation, specifically including the presence of variceal bleeding, hepatic encephalopathy, diuretic-resistant ascites, and/or jaundice with bilirubin >2.5 mg/dL. The pooled HR was 0.54 (95% CI, 0.46–0.65) with no heterogeneity between studies. Despite that, the quality of the evidence is low. Lastly, four studies evaluated the effects of statins on mortality in patients with

chronic liver disease with 2,011 statin users and 53,263 nonusers (16). Based on the three observational studies that assessed this outcome, the pooled HR was 0.67 (95% CI, 0.46–0.98) with significant heterogeneity. The HR of mortality in the only RCT included was 0.39 (95% CI, 0.15–0.99). The protective effect of statins on mortality in patients with chronic liver disease is considered as very-low quality of evidence.

Kamal *et al.*'s systematic review and meta-analysis is very well constructed and conducted. Their methods are clearly described and transparent. It also attempts to answer a significant question that has the potential to have a major impact on how we treat patients with cirrhosis. Although these findings are very encouraging and are based on a very large number of patients, the quality of a meta-analysis is only as good as the quality of the studies included. In this case, out of ten publications, only one is considered as high quality of evidence. Furthermore, this study is based on a small number of patients where 69 patients received a statin and 78 did not (15). Furthermore, most of the studies included involved patients with HCV and although they tried to adjust for certain variables such as the MELD score, and Child-Pugh score at baseline, it is unclear what proportion of patients were treated with new direct acting antiviral (DAA) treatment. HCV related therapy, especially if during the follow-up time, is an important confounder as achieving sustained virological response (SVR) can itself slow down and even reverse some degree of hepatic fibrosis. Regardless, statins have also been shown in *in vivo* and *in vitro* models to modulate the effects of HCV on the liver by blocking a necessary step in viral replication, decreasing viral entry into hepatocytes. In the pre-DAA era, statin users achieved higher rates of SVR than nonusers (39.2% *vs.* 33.3%, $P < 0.01$) (18). Nonetheless, the impact of statins in this patient population is significant and consistent amongst the identified studies.

One of the most important concerns with the widespread and indiscriminate use of statins in patients with chronic liver disease has been the safety of these medications in this vulnerable patient population. In a large UK primary healthcare based setting, the crude incidence of moderate or serious liver dysfunction was between 15.19 to 17.37 per 10,000 patient years (19). In a prospectively maintained drug-induced liver injury (DILI) database, statins were the cause of DILI in 3.4% of cases (20). Their database identified atorvastatin as the 18th leading cause of DILI at their center. There is no evidence from large registries that cirrhosis confers an additional risk for hepatotoxicity

when using statins. In the BLEPS study, the incidence of any adverse events was similar between the placebo and the simvastatin treated group, in 75.9% vs. 81.4% of cases respectively (15). Treatment-related adverse event was attributed to statin use in 22.8% of cases, and in 17.7% of patients in the placebo group. Serious and treatment-related adverse events were noted in 10.8% vs. 8.0% of cases in the placebo and simvastatin group respectively. Only 1 patient in the simvastatin group developed increased liver transaminases more than 3 times the upper limit of normal. After discontinuing the medication, the abnormality resolved. Two patients with Child Pugh B/C cirrhosis developed rhabdomyolysis which led to discontinuation of simvastatin. Both conditions resolved upon cessation of the medication. This is why a careful risk benefit assessment has to be performed before initiating patients with decompensated liver disease, particularly those with Child-Pugh B or C cirrhosis. Furthermore, if initiated, regardless of the indication, close monitoring of liver enzymes, and creatinine kinase should be performed.

In conclusion, the repurposing of statins for the benefit of patients with chronic liver disease and portal hypertension is highly attractive (8). Based on the available evidence to date, it would slow fibrosis progression, decrease rates of hepatic decompensation, and improve mortality. Unfortunately, these conclusions stem from low quality evidence retrospective observational studies. It is therefore imperative that, before we can implement statins in the treatment algorithm of patients with cirrhosis and portal hypertension, adequately powered high quality randomized clinical trials be conducted with an emphasis on efficacy end points such as hepatic decompensation and liver related mortality, and safety. In our opinion the group of patients with the greatest potential benefit is those with compensated cirrhosis and CSPH. Until data from randomized studies are available, the use of statins in patients with advanced liver disease remains largely investigational.

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