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INVITED COMMENTARY

Statins in Cirrhosis: Trial Data Are in but the Jury Is Still Out

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Hepatic decompensation, particularly when complicated by the development of ascites and/or variceal hemorrhage, demarcates an inflection point in the natural history of advanced chronic liver disease (ACLD). Although patients who maintain compensated status (cACLD) generally maintain near-normal life expectancy, patients with decompensated (dACLD) progress rapidly to liver transplantation or death within 1–3 years [1]. The presence of clinically significant portal hypertension, defined by a hepatic vein wedge pressure gradient ≥ 10 mmHg or estimated by non-invasive assessments, such as platelet count or liver stiffness measurements by elastography, remains the primary risk factor for incident hepatic decompensation [2]. Medical lowering portal pressure, primarily through the use of non-selective beta-blockers, reduces the risk of incident decompensation, improving long-term outcomes [3].

Unfortunately, not all patients are candidates for or tolerate non-selective beta-blockade, leading to the search for other medical therapeutic strategies to lower portal pressure. A leading candidate medication class is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-coA) reductase inhibitors, commonly referred to as statins. Statins, independent of their primary function of lowering serum cholesterol to reduce the risk of cardiovascular disease, increase the activity of endothelial nitric oxide synthase (eNOS) with resultant vasodilation and reduced portal pressure [4]. As reviewed elsewhere, statins exert additional anti-inflammatory effects that may reduce vascular inflammation [4] and subsequent fibrogenesis [5]. These potential in vivo salutary effects combined with data from encouraging single-center prospective studies [6] have accelerated the initiation of several large multicenter studies designed to determine the potential application of statins to prevent hepatic decompensation [7] or improve outcomes in decompensated subjects [8].

In this issue of *Digestive Diseases and Sciences*, Munoz et al. [9] from Buenos Aires, Argentina hypothesized that the anti-inflammatory effects of statins would improve the natural history of cirrhosis. To test this hypothesis, the investigators treated 30 patients with cirrhosis, primarily Child–Turcotte–Pugh (CTP) class B, with simvastatin 40 mg daily for one year to evaluate the effect of statin therapy on CTP score. The safety outcomes of this uncontrolled Phase IIA study have been previously published [10]. Notably, adverse effects were common, including dose-related muscle injury in 11/30 that required dose reduction or interruption. Two CTP C patients exhibited myonecrosis but did not meet criteria for rhabdomyolysis. Gastrointestinal toxicity was also commonly observed, although statins showed no significant hepatotoxicity. In this secondary analysis, the investigators explored changes in clinical status, laboratory parameters, and health-related quality of life. During the study period, 12 patients initially characterized as CTP B improved to CTP A, whereas only 3 patients initially characterized as CTP A worsened to CTP B. A significant increase in serum albumin, a component of the CTP score, was observed in the treated patients, predominantly those that finished the study as CTP A, with baseline serum albumin levels > 3.0 g/dl associated with either maintenance of, or improvement to, CTP A status. Among patients with improved or maintained CTP A status, there were improvements in physical functioning and body pain.

Although the improvement in clinical staging observed is encouraging, the small sample size and single-arm study design does not support conclusions regarding the clinical efficacy or anti-inflammatory effects of statins. Access to hepatitis C direct antiviral therapy and alcohol use counseling with longer periods of sobriety in the observed patients could also explain these clinical improvements. While the parent trial reported 13% of patients were self-reported active drinkers, formal alcohol metabolite testing frequently identifies significant alcohol use in a large fraction of patients. Dietary modification and diuretic therapy

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could have also improved the CTP ascites subscore independent of medication effect. That patients with better preserved albumin levels seemed to have superior outcomes and fewer adverse events in the present study suggests that the safe window to utilize statins in cirrhosis may be among the compensated subset. Nevertheless, this observation could also reflect confounding by indication, in which patients with better preserved liver function at baseline are likely to have superior outcomes irrespective of treatment assignment.

Two CTP C patients developed myonecrosis in this study; it was only patients with CTP C cirrhosis in the Bleeding Prevention With Simvastatin (BLEPS) trial that developed rhabdomyolysis [6]. In future trial design and in clinical practice, patients with CTP C cirrhosis or total bilirubin ≥ 3 mg/dl should not be initiated on statins and if already taking should discontinue therapy. The 40 mg dose of simvastatin used in the present study was subsequently associated with high rates muscle and liver toxicity in CTP B patients [8] and should not be prescribed in decompensated patients. Although simvastatin 20 mg does appear to retain reasonable safety in CTP B, no data exist to inform safe maximal doses for other statin preparations, such as atorvastatin, rosuvastatin, or pravastatin.

Thus, while the present study suggests a general trend toward clinical improvement using statins in patients with CTP A and B cirrhosis, the jury remains out. It is hoped that within the next several years, data obtained from larger randomized trials will provide more definitive justification for broad utilization of statins in compensated and perhaps early decompensated ACLD patients. For now, optimization of diet, minimization of risk factors, such as alcohol and obesity, and selective application of non-selective beta-blockers remain the most prudent interventions in cACLD patients in the clinic.

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Declarations

Conflict of interest The author declares that there is no conflict of interest to disclose.

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