Editorial Commentary

Statins in patients with cirrhosis: a note of caution in the middle of hope

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In the last decade, use of statins by patients with liver disease has undergone a profound change. These medications, originally used for the treatment of dyslipidemia, have been previously described as potentially hepatotoxic, and consequently entailed restricted use for patients with liver disease (1,2). Nevertheless, lipid disorders are quite frequent in this population, particularly in those with non-alcoholic fatty-liver disease and primary biliary cirrhosis. The first studies conducted in these populations showed that statins were safe and well tolerated and that they should no longer be contraindicated for the treatment of dyslipidemia in these populations (3,4).

Apart from effects on lipid metabolism, statins have other notable properties that may be of interest in these patients. In animal models of chronic liver disease, these drugs have shown anti-inflammatory, antifibrotic and portal pressure-reducing effects (5-7). Clinical studies, mostly retrospective and observational, have associated the use of statins with a decrease in both the rate of progression to cirrhosis and incidence of hepatocellular carcinoma (8). However, the vast majority of patients in these studies did not have cirrhosis. Studies specifically conducted in patients with cirrhosis (most of them in compensated stage) show that, when given in combination with beta-blockers for variable periods (1–12 months), statins can reduce portal pressure (9-12). Interestingly, in the largest of these studies, use of simvastatin was associated with decreased mortality, mainly due to lower rates of infection and renal failure, but not recurrent variceal upper gastrointestinal bleeding (12). These findings highlight statins as a promising drug for the prevention of further decompensation and acute-on-chronic liver failure (ACLF), as infections are a frequent predisposing event, especially in western populations, and kidney is the single most important organ failure (13). ACLF has been recognized as a threating complication in patients with cirrhosis, with high short-term mortality and no specific treatment approved so far, other than organ failure support (14). Interventions aimed at ACLF prevention are of paramount importance and urgently needed.

One important question is the safety of drugs in advanced liver disease patients. Drug metabolism may suffer profound alterations depending on the extent of portal hypertension and liver failure. In the majority of registry studies, liver disease and specifically cirrhosis, is an exclusion criterion. In general populations, liver and muscle toxicity have been described in up to 3% and 9% respectively and cases of severe liver and muscle toxicity due to statins have been described in patients with cirrhosis. The true frequency of these complications and their relation with severity of liver failure in patients with decompensated cirrhosis are largely unknown. Therefore, studies specifically conducted in these patients are needed before general recommendation of drug usage in this population.

In a study recently published in *Lancet Gastroenterology and Hepatology*, Pose *et al.* evaluated the safety of a 2-dosage combination of Simvastatin and Rifaximin in patients with decompensated cirrhosis (15). The study is one of the first publications of a large project designed to evaluate this combination as a prophylaxis of progression of cirrhosis

and development of ACLF. The authors theorize that the addition of rifaximin, a non-absorbed antibiotic used for the prevention and treatment of hepatic encephalopathy, might reduce the incidence of complications of cirrhosis and mortality. Rifaximin has been associated with beneficial effects in gut-derived endotoxin level and kidney function in some studies (16), but not others (17). This combination has not been evaluated in prospective studies. Also, all previous studies in cirrhotic patients combined statins with beta-blockers, and it is not known if the use of statins alone can reduce portal pressure or attain the same useful clinical effects as in combination.

Liver and muscle toxicity were evaluated in 2 ways, as either differences in terms of increased liver and muscle enzymes between groups as well as the proportion of patients fulfilling pre-established definitions of DILI and rhabdomyolysis. The group of patients who received 40 mg of simvastatin plus rifaximin showed more pronounced elevations in ALT and AST, but not of Alkaline Phosphatase, when compared to 20 mg/day and placebo group. These increases were precocious, developing within 2–4 weeks of drug use. Additionally, 3 patients (19%) in the higher simvastatin dose group met the diagnostic criteria of DILI, while none of the patients in the other groups did. Information regarding the proportion of patients with elevations in ALT and/or AST not fulfilling DILI criteria are lacking. One may wonder if these patients really did develop DILI or if this was due to muscle toxicity. Elevations were more notable for AST, an enzyme more abundant in skeletal muscle than ALT. Also, all 3 patients had coincidental elevations in CK levels and were described as having concomitant rhabdomyolysis. To further corroborate the possible muscular origin of these elevations, the increase in AST had the same duration as that of creatinine kinase in two of the patients. Apart from an increase in INR in one patient, authors did not provide further details of liver function tests at the time of diagnosis and liver biopsy was not performed. This information would clarify the real nature of liver enzyme elevation in these patients.

Muscle toxicity was also common in the high simvastatin dose group. Elevations of CK were more prominent in these patients, with a median increase above 800%, and 3 patients developed rhabdomyolysis. There was no correlation of muscle-related symptoms or polymorphism of *SLCO1B1* gene and frequency of rhabdomyolysis, despite all patients with rhabdomyolysis being symptomatic at the time of diagnosis. Interestingly, 2 of 3 cases of muscle toxicity developed in Child-Pugh C patients. There is also no data with respect to kidney involvement in these patients, even though the authors state that no patients developed renal failure. The use of ICA-AKIN criteria for diagnosis and staging of kidney injury, as recommended by most international societies, as well as information regarding urine sediment and evolution of serum creatinine, would add further information to the frequency and relevance of kidney involvement, an important consequence of rhabdomyolysis, in this population.

Despite these reservations, the study brings us important information. The first important aspect addressed is the safety of a potential hepatotoxic drug used in patients with decompensated cirrhosis. Simvastatin and atorvastatin have unique pharmacokinetic properties that may render them more toxic in patients with advanced liver disease. They are metabolized in the liver by the cytochrome P-450 CYP3A4 system and are highly protein bound. In general populations, toxicity seems to be dose-dependent, as highlighted by a randomized trial of 80 versus 20 mg of Simvastatin for lowering LDL-cholesterol (18). Similar dose-dependent toxicity seems natural in patients with liver disease and dose-finding studies certainly add valuable information for this specific population, as demonstrated by the current study.

The rate of liver and muscle toxicity are much higher than previously reported, even for those including only patients with cirrhosis. This may be due to the fact that the current study is the only one exclusively including patients with decompensated cirrhosis. Higher frequency of muscle toxicity in Child-Pugh C patients further corroborates this impression.

Other factors could explain this high frequency of muscle toxicity. Simvastatin was given together with rifaximin, a drug associated with the development of rhabdomyolysis in cirrhotic patients in rare cases (19,20). The probable explanation is increased gastrointestinal absorption and a direct toxic effect of the drug in muscle tissue. Another possible explanation is that patients with liver disease may be at increased risk of muscle injury. It has long been recognized that muscle cramps, defined as involuntary painful contractions of a muscle, are common in cirrhosis, being described in up to 88% of patients (21). Alterations in energy metabolism leading to depletion of taurine (the most abundant amino acid in skeletal muscle tissue) and ATP are described in these patients and may be indirect evidence of a diseased muscle (22,23). Furthermore, cramps correlate with plasma renin activity and ascites, which are signs of

advanced disease (24). Cirrhotic patients may develop rhabdomyolysis spontaneously in more than 50% of cases and these may recur in one third of patients (25). The use of a combination of potential myotoxic drugs in a particularly vulnerable population may explain this unexpectedly high frequency of rhabdomyolysis.

In conclusion, the liver and/or muscle toxicity in cirrhotic patients receiving simvastatin at 40 mg/day is common and may be particularly high in those classified as Child-Pugh C. These findings indicate that simvastatin at a dose of 20 mg/day be adopted in decompensated cirrhosis in future clinical studies and also in clinical practice, with strict clinical and laboratory monitoring for side effects. It remains to be determined if this smaller dose is also safe in the long term and attains the clinical benefits previously demonstrated in studies using 40 mg/day. We may be facing with statins a situation similar to that experienced with beta blockers almost one decade ago, a moment in which the concept of a window of opportunity instead of widespread use was recognized. Until more data is available, statins should be used with extreme caution in decompensated cirrhosis.

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