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ABOUT COVER

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Addition of statins to the standard treatment in patients with cirrhosis: Safety and efficacy

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Abstract

This review summarizes the safety and efficacy of statins in patients with cirrhosis. Due to concerns about the safety of statins in patients with impaired liver function, they have recently been investigated as a potential treatment option in cirrhosis. The most clinically significant adverse event is statin-related myopathy, and this may be related to the high serum statin concentrations in the setting of severely impaired liver function. Rhabdomyolysis is the most serious and potentially life-threatening manifestation. It has recently been demonstrated that the recommended dose of simvastatin in patients with decompensated cirrhosis would be 20 mg/d because higher values, such as 40 mg/d, are associated with many adverse events, especially muscle injury. Likewise, simvastatin should not be administered to patients with Model for End-stage Liver Disease score > 12 and/or Child-Pugh class C because of the high risk of severe muscle injury. Due to the pleiotropic effects, the focus on statins has shifted from being considered harmful to something useful. Through these effects, statins could prevent liver-related morbidity and mortality in cirrhotic patients. Observational studies in large populations of patients with cirrhosis have shown that treatment with statins to decrease high cholesterol levels was associated with a reduced risk of hepatic decompensation, hepatocellular carcinoma development and death.

The few randomized controlled trials in patients with cirrhosis and portal hypertension showed that statins lower portal pressure, quite likely through a reduction in hepatic resistance. Another large randomized controlled trial in patients with variceal bleeding showed that simvastatin in addition to standard of care did not prevent rebleeding but improved survival rate. Despite these encouraging outcomes, the quality of the evidence regarding the use of statins is low or very low due to the observational characteristics of most of the studies involved. Therefore, it is advisable to perform further randomized controlled trials on a large series of patients with hard clinical endpoints, using different statin types and varying doses. The objectives would be to prevent liver-related morbidity and mortality rather than treating cirrhosis complications to take additional information that makes it possible to add statins to the standard of care of these patients.

Key Words: Cirrhosis; Liver disease; Statins; Safety; Efficiency

Core Tip: Several observational studies of statins in patients with liver disease were published, but they were highly biased. On the other hand, only one randomized controlled trial improved survival in Child-Pugh class A/B patients but did not reduce variceal rebleeding. Finally, the dose and type of statin to be used should be defined. This review concludes that new randomized controlled trials are necessary before endorsing statin use in patients with chronic liver disease.

INTRODUCTION

The 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, "statins," have been used for more than three decades to treat the increase of serum cholesterol by inhibiting its synthesis *via* the competitive inhibition of the hepatic enzyme HMG-CoA reductase [1]. They represent a breakthrough in the treatment and prevention of atherosclerotic cardiovascular disease. High-quality evidence from large randomized controlled trials (RCTs) supports the use of statins in primary and secondary prevention of atherosclerotic cardiovascular disease[2-5]. Nevertheless, no patients with liver disease were included in these trials, and consequently there is limited data regarding the therapeutical role of statins over this population.

Atherosclerosis has been widely recognized as an inflammatory process[6]. Statins prevent inflammatory atherosclerotic cardiovascular disease by two mechanisms: the first one is direct and acts by reducing the plasma cholesterol levels, and the second one is indirect and independent of cholesterol levels, also known as the pleiotropic effect. This effect reduces atherosclerotic inflammation independently of the serum cholesterol levels and any cholesterol levels variation[7,8]. The isoprenoid intermediates, such as farnesyl-PP and geranylgeranyl-PP, are essential in the biosynthetic pathway of cholesterol. These isoprenoid intermediates lead to isoprenylation, adding lipophilic molecules to various proteins, including the small guanosine triphosphate binding proteins Rho, Ras, and Rac (also known as small GTPases), which are activated and translocated from the cytoplasm to the cellular membrane. The inhibition of isoprenylation of Rho, Ras, and Rac by statins keeps them inactive in the cytoplasm, as shown in Supplementary Figures 1 and 2. The inhibition of isoprenoid intermediates favors the pleiotropic effects of statins by preventing small GTPase protein isoprenylation, implicated in intracellular signaling pathways[8].

Moreover, the activity of Rho kinase is reduced by the inhibiting effect of statins upon both hepatic stellate cells (HSC) and liver sinusoidal endothelial cells[9]. In experimental models, these effects seem to reduce collagen production and the activation of HSC in early fibrosis and proliferation, cytokine production and contraction of activated HSCs in cirrhosis[9,10]. Additionally, statins might decrease the turnover of HSCs inducing the senescence of these high activity cells[9-11]. On the other hand, in cirrhotic livers, statins improve endothelial dysfunction by the upregulated activity of endothelial nitric oxide synthase and nitric oxide availability and lower portal pressure[9,12]. Krüppel like factor 2 mediates statin-induced upregulation of endothelial nitric oxide synthase to decrease HSC activation and produce a further decrease of portal pressure[13,14]. These data deliver the rationale for statin use in patients with cirrhosis and portal hypertension[15,16].

This review will discuss available evidence about the safety and efficacy of statins in patients with cirrhosis.

SAFETY

The most commonly reported adverse events during treatment with statins are relatively mild and often described as transient gastrointestinal symptoms (diarrhea, abdominal pain, flatulence and constipation), headache and rash[17]. Muscle injury, liver injury and new-onset diabetes mellitus are proven adverse events of statin therapy[18]. Statin plasma levels have been regarded as an index of these potential adverse events[19], and they depend on several factors[20]:

(1) Statin dose: High-intensity statin therapy reduces cardiovascular events more than lower intensity equivalent treatment, but the safety impact of using the first one is unknown. On that subject, a meta-analysis showed that high-intensity statin therapy augmented the incidence of increased aminotransferase levels [relative risk = 3.10; 95% confidence interval (CI): 0.88-7.85] compared with lower intensity statin therapy. Based on clinical trials, the authors conclude that an aggressive statin therapy increases aminotransferase levels more than a lower intensity one[21].

(2) Statin type: In a rat model, Nezasa *et al*[22] showed that rosuvastatin was taken up by hepatocytes more selectively and more efficiently than simvastatin. A possible reason for this finding is that rosuvastatin requires an anion transporter to enter into the cells in the same way as pravastatin, another hydrophilic statin. On the other hand, simvastatin does so by passive diffusion. This possibly happens due to its greater lipophilicity, and in this way, it is similarly taken up by the liver and by extrahepatic tissues as other lipophilic statins do, such as atorvastatin and fluvastatin. These different mechanisms of entry into the cells may be consistent with specific organ toxicity.

In the meta-analysis mentioned above, when evaluating the different effects of hydrophilic and lipophilic statins were studied, higher intensity therapies based on the first ones showed an increased risk for raising aminotransferases levels, whereas those using lipophilic statins did not. Regarding creatine kinase (CK) levels, these were not increased during evaluating hydrophilic statins, whereas lipophilic statins revealed an increased risk with higher intensity treatment[21]. Therefore, the increase in aminotransferase levels is likely to be more troublesome when high doses of hydrophilic statins are prescribed, whereas CK elevations become problematic with equally aggressive lipophilic statin treatment.

(3) Drug-drug interactions: Drug interactions that involve statins may be enhanced in the setting of cirrhosis, given the altered statin pharmacokinetics[23]. In this sense, the total body clearance of statins is very high due to the important hepatic first-pass effect. Except for pravastatin metabolized enzymatically in the liver cytosol, all statins undergo extensive microsomal metabolism by the cytochrome P450 isoenzyme systems[20]. The cytochrome 4503A4 isoform commonly has a competitive inhibition with drugs at the enzymatic level and may alter statin disposition, leading to increased plasma levels and greater risk of adverse events[24]. Since 2011, the United States Food and Drug Administration is assuming a more significant role in post-marketing surveillance and keeping package labeling of statins with current contemporary literature[25]. In Supplementary Table 1 are shown simvastatin-drug interactions[26]. This information is deemed incomplete, therefore an updated bibliography and other tools for evaluating the interaction with each drug are needed. It is important to note that there are no simvastatin interactions with drugs commonly used in cirrhosis, such as non-selective β-blockers (NSBBs), diuretics, quinolones, rifaximin and anticoagulants.

Also, the consumption of grapefruit juice, at more than 1 quart per day (approximately 1 L/d), is known to inhibit cytochrome 3A4 isoenzyme activity in the enterocyte[27]. Likewise, gemfibrozil therapy reduces glucuronidation and consequently the elimination of statins[28]. Therefore, the effect of both could increase statin availability and in turn potentially raise their systemic exposure and side effect occurrence.

(4) Reduced statin metabolism and/or transport activities: It is well known that cirrhosis significantly affects statin pharmacokinetics[29]. However, although no study has so far evaluated the pharmacokinetics of simvastatin in cirrhotic patients, there are data with other statins in Child-Pugh (CTP) class A and class B patients[30-32]. So far, there are no reports about the pharmacokinetics of statins in CTP class C patients. It is known that the maximum plasma concentration increases with rosuvastatin, the area under the curve becomes larger with fluvastatin and both parameters increase with atorvastatin in cirrhosis[30-32]. Furthermore, another mechanism could be a single nucleotide polymorphism in SLCO1B1, which encodes the OATP1B1 that regulates the hepatic uptake of statins[33]. Recent studies have shown that a diminished expression of SLCO1B1 is associated with progressive alcoholic liver disease[34,35]. This last mechanism reduces the hepatic uptake and increases the blood levels of statins and enhances the risk of adverse events[19].

Proven adverse events

Muscle injury: Statins have been associated with a broad spectrum of muscle injury ranging from asymptomatic serum CK elevations to rhabdomyolysis[36]. Statin-associated muscle adverse events ranged from 1% to 5% in controlled clinical trials and 11% to 29% in observational ones[36]. Much of the concern about statin's potential side effects arise from the results of these observational studies.

There are well-established risk factors for statin-related muscle injury[36]. Mounting evidence suggests that higher-dose statin therapy confers a greater risk of muscle injury (see Safety, Statin dose). Statin-related muscle injury is also related to interactions between drugs that increase serum statin levels (see Safety, Drug-drug interactions).

Many patients experience the onset of symptoms in a temporary relationship when starting statin therapy. These symptoms often carry patients and physicians to claim that statins are the cause for them, even when there are very few randomized data to support these assertions. The N-of-1 trial in a group of eight patients experiencing myalgia while being treated with statins demonstrated that data on subjective side effects from observational studies are heavily loaded with bias. Patients were randomly assigned to receive either placebo or the same statin; each patient served as their self-control, and statin and placebo were alternated between them. Pain and interference with life activity were assessed using a weekly visual analog scale. The authors observed no significant difference between statin and placebo in myalgia score in each patient, with five patients resuming statin therapy[37].

Muscle safety in patients with cirrhosis was assessed in three RCTs that evaluated the effect of simvastatin on portal pressure and gastrointestinal bleeding occurrence [16,38,39]. These studies included patients from all CTP classes, but the proportion of CTP class C patients was low. Abraldes *et al*[16] reported a 2-fold increase — or higher — in CK levels for 1 out of 29 placebo patients and 2 out of 30 simvastatin patients. They concluded that the simvastatin safety profile was excellent. Pollo-Flores *et al*[38] reported a 7% incidence of myalgia in the simvastatin group and a 10% in the placebo group. Finally, in BLEPS (Bleeding Prevention with Simvastatin) trial, when evaluating the addition of simvastatin to standard therapy for preventing variceal rebleeding, 2 out of 69 patients on simvastatin developed rhabdomyolysis (2.9%)[40], which was a concerning issue considering an incidence of 0.009% to 0.1% in the general population [41]. The authors observed that both patients had a more advanced liver disease with bilirubin levels greater than 5 mg/dL. Therefore, Abraldes *et al*[16] concluded that severely deteriorated liver function patients might develop muscle injury at lower doses than the general population.

The LIVERHOPE-SAFETY trial was a double-blind, randomized, placebo-controlled, phase 2 trial in patients with decompensated cirrhosis and moderate-to-severe liver failure from nine university hospitals in six European countries[42]. Patients older than 18 years with CTP class B or class C disease were eligible and randomly assigned to receive for 12 wk (in a 1:1:1 proportion) either: Simvastatin 40 mg/d plus rifaximin 1200 mg/d (SVT40 + RFX), simvastatin 20 mg/d plus rifaximin 1200 mg/d (SVT20 + RFX) or placebo of both drugs. Randomization was stratified according to CTP class (B *vs* C). The main endpoint was the appearance of liver or muscle injury, as defined by changes in aspartate aminotransferase (AST) and alanine aminotransferase

(ALT), alkaline phosphatase and CK. The full analysis set included 44 patients: 16 in the SVT40 + RFX group, 14 in the SVT20 + RFX group and 14 in the placebo group. Patients in the first group showed an increase in CK at the end of treatment compared with patients in the placebo group (1060 IU/L *vs* 106 IU/L, *P* = 0.014). It was also observed that there were no significant changes in CK levels in the second group *vs* the placebo group (106 IU/L *vs* 67 IU/L, *P* = 0.992). Three patients (19%) from the SVT40 + RFX group developed liver and muscle toxicity consistent with rhabdomyolysis. See Safety, Reduced activities in statins metabolism and/or transport.

Liver injury: An electronic PubMed search of reported statin hepatotoxicity cases identified 40 patients in 26 publications[43]. The small number of reported cases is a testimony of the supposed hepatic safety of statins given many recipes for this class of drugs, *e.g.*, 142 million in 2008 in the United States alone[44]. Of the 40 cases, 17 patients were men, and most in the sixth or seventh decade of life. The initial symptoms were jaundice, anorexia, nausea, abdominal pain, adynamia and pruritus, similar to acute hepatitis. Mortality due to statins was exceptionally infrequent because only two cases were reported[45,46]. The time elapsed since the drug administration and the development of hepatotoxicity is highly variable: between 5 d and 4 years. However, in more than half of the cases, it occurred within 4 mo from the start of therapy. The interval between the discontinuation of the statin and drug-induced liver injury resolution ranges from a few weeks to 6 mo. The most frequent liver damage pattern is hepatocellular; however, a mixed pattern was also reported, with prolonged symptomatic cholestasis[47].

Based on this data, the Food and Drug Administration in 2012 issued a report on significant changes in the safety of the statin packet insert; all statins currently marketed appear to be associated with a shallow risk of severe hepatic injury[48]. Furthermore, continuous periodic monitoring with ALT does not help detect or prevent drug-induced liver injury and removes the need to perform it. Packet inserts now recommend performing liver function tests before starting statin therapy and then when clinically indicated.

Three RCTs that appraised the effect of simvastatin on portal pressure and gastrointestinal bleeding frequency assessed the liver safety of statins in patients with cirrhosis[16,38,40]. Pollo-Flores *et al*[38] did not report any patient with liver injury. Abraldes *et al*[16] observed a patient with aminotransferase increase in each trial. In 2009, with AST > 2 times the upper limit of the normal, simvastatin was continued, whereas in 2016, with ALT > 3 times the upper limit of the normal, simvastatin was stopped[40].

In the LIVERHOPE-SAFETY trial, due to advice from the data safety monitoring board, the SVT40 + RFX group was stopped prematurely when the first 10 patients completed treatment because of severe liver adverse events (grade 3)[42]. Patients within the SVT40 + RFX group showed a significant increase in AST and ALT than the placebo group (AST 191 IU/L *vs* AST 62 IU/L, *P* = 0.0009 and ALT 96 IU/L *vs* ALT 35 IU/L, *P* = 0.0025). They observed no significant differences at 12 wk in AST and ALT between the SVT20 + RFX and placebo groups (AST 48 IU/L *vs* AST 62 IU/L, *P* = 0.728 and ALT 27 IU/L *vs* ALT 35 IU/L, *P* = 0.698, respectively). There were no significant differences in alkaline phosphatase levels between the SVT40 + RFX or the SVT20 + RFX groups compared with the placebo group. The number of patients who stopped treatment because of adverse events was significantly higher in the SVT40 + RFX group [9 (56%) of 16 patients] compared with the other two groups [2 (14%) of 14 for both groups, *P* = 0.017]. In conclusion, in patients with decompensated cirrhosis, SVT40 + RFX was associated with a significant increase in adverse events requiring treatment withdrawal, specifically liver and muscle toxicity, compared with SVT20 + RFX. In future trials evaluating the role of statins in patients with decompensated cirrhosis, simvastatin 20 mg/d should be preferred to 40 mg/d. See, Safety, Reduced activities in statins metabolism and/or transport.

EFFICACY

Statins and risks of cirrhosis decompensation and death

Cirrhosis is a worldwide public health problem, together with its complications and hepatocellular carcinoma (HCC). In this regard, evidence from preclinical and clinical research of drugs such as statins showed a potentially positive effect on the natural history of cirrhosis[49].

The evaluation of these issues was performed based on large-sized national registries. These trials were derived from detailed patient databases in which the International Classification of Diseases, 9th version codes identified variables of interest. Patients treated with statins during follow-up were compared with those not treated with them, and endpoints were adjusted for the most important confounding variables. Simvastatin was the most frequent statin used in all studies. The majority of studies carried out unmatched analysis together with propensity score (PS)-matched analysis. Statins consistently reduced the risk of cirrhosis decompensation and death (Table 1).

Supported by data taken from the Veteran Affairs Clinical Case Registry, the use of statins within patients with hepatitis C virus (HCV) and compensated cirrhosis is related to a 40% or higher reduction in the risk of cirrhosis decompensation and death [50]. Huang *et al*[51] showed that patients with chronic hepatitis B who received statin had a dose-dependent reduction in the risk of cirrhosis complications. Patients with hepatitis B virus (HBV)-, HCV- and alcohol-related cirrhosis were identified from a Taiwan National Health Insurance[52]. Statins, in a dose-dependent manner, decrease the decompensation rate in both HBV- and HCV-related cirrhosis. For patients with alcohol-related cirrhosis, a decreased decompensation rate has a borderline significance. In a low number of patients with biopsy-proven cirrhosis, Kumar *et al*[53] demonstrated that statins delay cirrhosis complications and reduce mortality. For patients with alcoholic cirrhosis, the use of statins showed an association with a reduced risk of decompensation and death. This association was stronger in patients with cirrhosis than in those with non-cirrhotic controls[54]. Statins consistently reduced the risk of decompensation and death in all studies, with hazard ratios ranging from 0.29 to 0.58 and 0.46 to 0.66, respectively[55].

Statins and portal hypertension

In the first RCT on the matter, Abraldes *et al*[16] assumed that pleiotropic effects are the rational basis for statin use in patients with cirrhosis and portal hypertension, which led them to conduct a proof-of-concept study, as shown in Table 2. A multi-center RCT evaluated simvastatin or placebo administration to patients with cirrhosis and severe portal hypertension for a month. The decrease in hepatic venous pressure gradient (HVPG) by simvastatin was significantly greater than the placebo changes. In the simvastatin group, 9 out of 28 patients (32%) *vs* in the placebo group, 3 out of 27 patients (11%) reached a target hemodynamic response defined as a reduction in HVPG of at least 20% of baseline values or to less than 12 mmHg ($P = 0.054$). The decrease in portal pressure observed with simvastatin was not associated with changes in hepatic blood flow. Simvastatin significantly decreased the HVPG in both sets of patients: those who received NSBBs and those who did not receive them. The portal pressure-reducing effect of simvastatin was slightly higher in patients receiving NSBBs than those who were not. Finally, simvastatin administration but not placebo markedly increased indocyanine green clearance, fractional clearance and intrinsic clearance, suggesting that simvastatin increased effective liver perfusion and improved liver function. In summary, this proof-of-concept study has shown that simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension, most likely through a reduction in hepatic vascular resistance without adverse effects on the systemic circulation and consistent with the theory that hemodynamic effects of simvastatin are liver-selective. Whether the patients are taking NSBBs or not, simvastatin decreases HVPG. This suggests that its effect on portal pressure is additive with the NSBBs. Besides, simvastatin improves liver function tests by enhancing effective liver perfusion and providing potential additional benefits to NSBB therapy.

The BLEPS trial is the largest RCT that assessed the effects of statins in cirrhosis. In patients with variceal bleeding, simvastatin was added to standard prophylaxis to prevent rebleeding — NSBBs and band ligation[40]. Within 10 d of bleeding, patients were randomly assigned to receive simvastatin 20 mg/d ($n = 69$) or placebo ($n = 78$) for the first 2 wk, followed by 40 mg/d or placebo for 2 years and stratified by CTP class A/B *vs* class C. The main endpoint was a composite of rebleeding or death. During a median follow-up of approximately 1 year, 30 out of 78 patients (39%) in the placebo group and 22 out of 69 patients (32%) in the simvastatin group reached the primary endpoint [hazard ratio (HR) = 0.82; 95%CI: 0.47-1.43, $P = 0.420$]. Nonetheless, when only death was evaluated, mortality was 22% in the placebo group compared to 9% in the simvastatin group (HR = 0.39; 95%CI: 0.15-0.99, $P = 0.030$). Therefore, treatment with simvastatin was associated with a 61% reduction in the relative death risk than placebo. Rebleeding, spontaneous bacterial peritonitis, and progression of liver disease were the most frequent cause of death in the placebo group (5, 3 and 3 patients, respectively), and in the simvastatin group, only one patient died by re-

Table 1 Statins, cirrhosis decompensation, hepatocellular carcinoma and mortality

Ref.	Groups, *n*	Follow up	Risk reduction
Mohanty *et al*[50], 2016	Statins 1323; Nonusers 12522	Approximately 2.5 yr for statin; Approximately 2.5 yr for nonusers	Cirrhosis decompensation and mortality
Huang *et al*[51], 2016	Statins 6543; Nonusers 6543	4.7 yr for statins; 4.6 yr for nonusers	Cirrhosis decompensation
Chang *et al*[52], 2017	Statins 1174; Nonusers 6453	Approximately 3.0 yr	Cirrhosis decompensation, HCC, and mortality
Kumar *et al*[53], 2014	Statins 81; Nonusers 162	Approximately 3.0 yr for statin; Approximately 1.5 yr for nonusers	Cirrhosis decompensation and mortality
Bang *et al*[54], 2017	Statins 794; Nonusers 4623	Approximately 4.0 yr	Cirrhosis decompensation and mortality

HCC: Hepatocellular carcinoma.

Table 2 Statins and portal hypertension

Ref.	Groups	*n*	Endpoints	Outcomes
Abraldes *et al*[16], 2009	SVT; Placebo	27; 28	Change in HVPG	HVPG decreased in SVT from 18.5 to 17.1, *P* = 0.003; no decrease in placebo
Pollo-Flores *et al* [38], 2015	SVT; Placebo	14; 20	Change in HVPG	HVPG decreased in SVT *vs* placebo: -2 *vs* 0 mmHg, *P* = 0.02
Bishnu *et al*[39], 2018	ATV + NSBBs; NSBBs	11; 12	Change in HVPG	HVPG decreased in ATV + NSBBs -4.8 *vs* NSBBs -2.6 mmHg, *P* = 0.041
Abraldes *et al*[40], 2016	SVT; Placebo	69; 78	Composite endpoint (rebleeding or death)	Non-significant decrease in risk of rebleeding or death; decrease in mortality HR = 0.39, *P* = 0.030 in SVT *vs* placebo
Wani *et al*[56], 2017	CVL; CVL + SVT	101; 35	Change in HVPG	HVPG decreased 62% in CVL and 16% in CVL + SVT (CVL non-responders)

ATV: Atorvastatin; NSBBs: Non-selective β-blockers; CVL: Carvedilol; HR: Hazard ratio; HVPG: Hepatic venous pressure gradient; SVT: Simvastatin.

bleeding, none by spontaneous bacterial peritonitis and three by a progression of liver disease. An exploratory analysis showed that mortality improvement was mainly related to decreased liver-related deaths [14 in placebo and 6 events in simvastatin; absolute risk reduction = 10.39% (95%CI: 0.26-20.51]. In the subgroup analysis, the effects of simvastatin on survival were quantitatively different in CTP class A/B patients from CTP class C patients. In CTP class A/B patients, an important outcome was the significant decrease in mortality with simvastatin, which was not observed in CTP class C patients (HR = 0.16; 95%CI: 0.05-0.27, *P* = 0.006), as shown in Table 2. The other major secondary outcome was rebleeding. In the placebo group, 22 patients developed rebleeding (28%) and 17 patients in the simvastatin group (25%). The rebleeding rate was not significantly decreased by the addition of simvastatin to standard therapy. Neither difference was observed in the rate of other secondary outcomes, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, portal vein thrombosis and need for rescue shunting, need for transfusion, liver transplantation and Model for End-stage Liver Disease (MELD) score between the two groups during the study period. The BLEPS trial demonstrated that the effect of adding simvastatin to the standard of care in patients who recover from an acute variceal bleeding episode improves survival without reducing the rate of other complications of cirrhosis.

Shortly after, two RCTs on small groups of patients reported the effects of statins on portal hypertension. Most of the patients, CTP class A and class B, had compensated cirrhosis, and very few were CTP class C. In one of these trials, simvastatin (at 40 mg/d for 3 mo) was evaluated *vs* placebo, whereas for the other trial, atorvastatin (20 mg/d for 1 mo) plus propranolol was tested *vs* propranolol alone on portal pressure estimated by HVPG[38,39] (Table 2).

In the first place, Pollo-Flores *et al*[38] showed that simvastatin therapy was associated with a decrease in HVPG, whereas no change was noted in the placebo group. Likewise, in 55% of patients treated with simvastatin, a clinically significant reduction in portal pressure was achieved because the decrease in HVPG was greater

than 20% *vs* no decrease in HVPG for patients with placebo (*P* = 0.030). Furthermore, they observed a slight improvement in liver function by CTP score, at baseline 6.6 *vs* at the end of the trial 6.2, *P* = 0.080. They concluded that simvastatin lowers portal pressure and may improve liver function.

Secondly, Bishnu *et al*[39] demonstrated that atorvastatin plus propranolol *vs* propranolol alone was associated with a greater decrease of HVPG mean. Likewise, the combined treatment compared with propranolol alone achieved more frequently a clinically significant reduction in portal HVPG (91% *vs* 50%, *P* = 0.069). However, they did not observe differences between the groups in cirrhosis complications and death after a 1 year follow-up. They concluded that the addition of atorvastatin to propranolol leads to a more significant reduction of portal pressure in patients with cirrhosis, likely through a reduction in hepatic vascular resistance.

In 2017, Wani *et al*[56] carried out a sequential trial in carvedilol non-responders to analyze if adding simvastatin could be a medical rescue therapy in these patients. One hundred and two consecutive patients with cirrhosis and significant portal hypertension were included. Forty-three were CTP class A, 32 were CTP class B and 27 were CTP class C. HVPG was measured at the baseline and after 3 mo of carvedilol treatment. Sixty-four patients (63%) responded to carvedilol. The other thirty-eight were classified as carvedilol non-responders. In these patients, simvastatin 20 mg/d was added for 2 wk, and after the adverse events were evaluated, 3 patients were discontinued. Thirty-five continued carvedilol and simvastatin 40 mg/d for up to 1 mo, and a new measurement of HVPG was performed. There were 16 responders (42%) and 19 non-responders. Thus, the overall carvedilol response was 79% (63% with carvedilol alone and 16% with carvedilol plus simvastatin), as shown in Table 2. In conclusion, this is the first time it has been clearly shown that a sequential treatment is an excellent strategy in the medical therapy of portal hypertension.

Statins and risk of infections

Infections are common in cirrhotic patients, and their presence causes a four-fold increase in mortality[57]. Motzkus-Feagans *et al*[58] assessed the consequence of including statins on the occurrence of infections. This trial was carried over 19379 compensated cirrhosis patients from the United States Veterans Health Administration database. Statins were administered to 2468 patients, simvastatin being the most common one. Infection was diagnosed in 200 statin users and 2153 nonusers during follow-up. The most frequent infections were pneumonia and skin infections. Statin treatment was associated with a reduction of infection rate and of mortality rate in the whole cohort (adjusted HR = 0.42; 95%CI: 0.36-0.48), and the PS-matched sample included 503 statin users and 1760 statin nonusers (adjusted HR = 0.67; 95%CI: 0.47-0.95). They concluded that statin use might potentially reduce the morbidity and mortality by infections in patients with cirrhosis.

Statins and risk of HCC

The World Health Organization (globacan.iarc.fr) estimated that HCC globally speaking is now the fifth most common type of cancer and the third cause of cancer-related mortality. Back in 2012, there were approximately 782000 cases, of which 83% were from the underdeveloped regions of the world[59]. Pre-existing cirrhosis was present in more than 80% of participants diagnosed with HCC[60].

The Electronically Retrieved Cohort of HCV Infected Veterans for the first time has shown that statin addition to pegylated interferon-based therapy for chronic HCV infection, decreases the incidence of HCC in those who received statin therapy compared to those who did not. Statins remained significantly associated with a lower risk of HCC incidence (HR = 0.51; 95%CI: 0.34-0.76)[61]. In an extension of their previous study, the authors showed that the decrease in HCC was dose-dependent. For subjects with 90-180 cumulative defined daily dose and cumulative defined daily dose > 180, adjusted HRs of incident HCC were 0.48 (95%CI: 0.27-0.88, *P* = 0.02) and 0.51 (95%CI: 0.36-0.72, *P* = 0.0001), respectively. Increasing statin dose was also associated with a significant delay in the time taken for the development of HCC. In two sensitivity analyses, it was shown that the incidence of HCC was independent of statin antifibrotic effect and sustained virological response[62].

Hsiang *et al*[63] ran a hospital-based population trial on HBV patients taken from the Hospital Authority database in Hong Kong. They defined statin use by landmark analysis to abrogate "immortal time bias" and PS to minimize baseline confounders and "indication bias." The 2-year landmark analysis entered 73499 patients with a crude HCC incidence of 1.75 per 100 patient-years. After landmark analysis and PS weighting of baseline covariates, statin users had a 32% risk reduction of HCC than nonusers. In subgroup analysis, a reduction of 59% in the HCC risk was associated

with concomitant statin and nucleos(t)ide analogues use compared to nucleos(t)ide analogues use alone. In conclusion, after adjustment for confounders and biases in this HBV cohort, statin use was associated with reduced HCC risk by 32%. The authors were able to see the additive HCC chemopreventive effect with the concomitant use of nucleos(t)ide analogues and statins. In 2018, Kim *et al*[64] investigated the risk of HCC after statin use in the whole population and patients at high risk for pre-existing diabetes or cirrhosis. A nationwide, nested case-control study was conducted with data from the National Health Insurance Service-Physical Health Examination Cohort 2002-2013 in the Republic of Korea. Individuals diagnosed with HCC, over 514000 participants, were matched with controls based on the follow-up, their sex and their age. Statin use was associated with a reduced risk of HCC development [adjusted odds ratio (aOR) = 0.44] than nonusers. The reduction in patients at risk was more significant in the presence of diabetes (aOR = 0.28) than in the absence of it (aOR = 0.53) and the presence of cirrhosis (aOR = 0.39) than in the respective absence (aOR = 0.42). In conclusion, statin use may have a beneficial inhibitory effect on HCC deve-lopment, particularly in patients at high risk for pre-existing diabetes or cirrhosis.

Statins have also been tried as concomitant therapy in patients with confirmed HCC. Two RCTs evaluated the role of statins in the treatment of advanced HCC. Japanese authors randomized 83 patients with non-resectable HCC undergoing transarterial chemoembolization (TACE) into pravastatin 40 mg/d group and control group. The mean survival rate resulted significantly longer in the pravastatin plus TACE group *vs* control group, over 18 mo *vs* 9 mo, respectively (relative risk = 0.35; 95%CI: 0.17-0.61, *P* = 0.005)[65]. These results were confirmed in a similarly designed German RCT that included 131 patients. Survival in the pravastatin plus TACE group was 20.9 mo compared to TACE alone group 12.0 mo, *P* = 0.003[66].

OUR EXPERIENCE

A safety prospective, open, uncontrolled phase IIa trial was recently published online ahead of print about chronic simvastatin treatment in patients with decompensated cirrhosis. This trial included 30 patients, CTP class A (*n* = 6), B (*n* = 22) and C (*n* = 2). The patients received standard treatment plus simvastatin 20 mg/d for 2 wk and after that simvastatin 40 mg/d up to 1 year[67].

Muscle injury was assessed according to the National Lipid Association Safety Expert Panel of the United States[36]. In total, 11 out of 30 patients (36%) developed muscle injury, of which 7 were classified as myalgia (23.4%) and the remaining 4 myonecrosis (13.3%). All of them were related to simvastatin. On the other hand, a significantly greater baseline MELD score was observed within the group with muscle injury (14.0 ± 3.6) than the group without muscle injury (11.4 ± 2.8) (*P* = 0.035). The receiver operating characteristic analysis revealed a cutoff value > 12 for baseline MELD score to differentiate patients with muscle injury from those without muscle injury. Moreover, the only two CTP class C patients included in the study developed myonecrosis.

No patient developed drug-induced liver injury according to the criteria proposed by Aithal *et al*[68]. One patient developed diabetes mellitus (3.3%). This rate is more significant than for the first time reported in the JUPITER trial (0.6%)[69]. Gastro-intestinal symptoms were recorded in 53.3% of patients. The rate of each of them was from 7% to 40%. This figure is more significant than reported with simvastatin in subjects without liver disease for all digestive symptoms (10% and each one of them from 0.7% to 2.5%)[17]. Simvastatin dosage was reduced exclusively by myalgia and transiently interrupted due to myonecrosis; thus, muscle injury was considered the only clinically significant adverse event.

In conclusion, chronic treatment with simvastatin 40 mg/d in patients with decompensated cirrhosis up to 1 year was associated with several adverse events, although no liver injury was registered. Moreover, muscle injury was the only clinically significant adverse event, which appears to be related to the simvastatin dosage and the degree of cirrhosis severity. Consequently, simvastatin 40 mg/d should not be prescribed in patients with cirrhosis MELD score > 12 because of a high rate of adverse muscle events and CTP class C patients due to potential severe muscle injury.

META-ANALYSIS AND EDITORIAL

A recent systematic review and meta-analysis discussed the impact of statins on fibrosis progression, hepatic decompensation and death in patients with chronic liver disease[70]. Ten trials spanning over 259453 patients were evaluated; most of the aforementioned studies were discussed in this review. Subjects receiving statins *vs* statin nonusers were associated with a reduction of all the previous endpoints mentioned. However, the quality of the evidence for these results was low or very low because nine out of ten studies were observational.

An editorial about this article highlights that the quality of these outcomes arises from the weakness of observational studies, selection or channelings bias, residual confounding, heterogeneity in the methods used to estimate fibrosis progression, the underlying population, lack of granularity regarding specific statin use, dose and the absence of information on adverse events of statins[71].

Finally, the authors proposed if the time has arrived to consider approving the use of statins in patients with liver disease to prevent liver-related morbidity and mortality. There are now experimental studies supporting the biological plausibility of hepatic protection, observational evidence of a beneficial effect and a limited number of RCTs demonstrating benefits. However, many unknowns remain, including the optimal statin to select and its dosing, particularly in patients with impaired liver function, and the risk of severe non-hepatic adverse events, such as rhabdomyolysis [71]. After Kamal *et al*[70]'s study in 2017, only the LIVERHOPE-SAFETY trial[42] and our safety study[67] provided some security data, as we will refer to in the Discussion and Conclusion. Nevertheless, the study by Kamal *et al*[70] encourages and supports the need for well-designed clinical trials to assess the benefits and safety of statins in this population.

CONCLUSION

In patients with cirrhosis, the most significant adverse event is statin-related myopathy, and it may be associated with high serum statin concentrations in the setting of severely impaired liver function. According to the LIVERHOPE-SAFETY trial findings, patients with decompensated cirrhosis should be treated with a lower dose of simvastatin, maybe 20 mg/d rather than 40 mg/d dose. For this reason, statins could be unsafe in CTP class C patients. Likewise, and based on the safety trial, we advise that a simvastatin dosage of 40 mg/d should not be prescribed in patients with cirrhosis MELD score > 12 and/or CTP class C patients due to potential severe muscle injury. In observational studies over large populations of cirrhosis patients, statins were associated with a reduced risk of hepatic decompensation, HCC development and death. However, the quality of the evidence of these studies is considered low or very low. The few RCTs in patients with cirrhosis and portal hypertension showed statins lower portal pressure, likely reducing hepatic resistance. The largest RCT demonstrated that the addition of simvastatin to standard therapy improved survival but did not prevent variceal rebleeding. For these reasons, before endorsing statins in patients with CTP class A/B cirrhosis to prevent liver-related morbidity and mortality, further RCTs should be performed over a larger number of patients with hard clinical endpoints using different statins and dosage[72,73].

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