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Liver (J Bajaj, Section Editor)

The Use of Statins in Patients With Chronic Liver Disease and Cirrhosis

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Abstract

Purpose of review Statins are drugs developed to treat hypercholesterolemia. Its use in patients with liver disease has been limited because one of its potential and most feared side effects is hepatotoxicity. However, there is robust evidence that supports the safety of statins in this population in the absence of severe liver dysfunction. In this review, we will summarize the efficacy and safety of statins in cirrhosis.

Recent findings Statins are effective in the treatment of dyslipidemia in patients with liver disease, because of their pleiotropic properties. These properties are independent of their effect on cholesterol levels, such as improving endothelial dysfunction or having antioxidant, antifibrotic, anti-inflammatory, antiproliferative, antiangiogenic, proapoptotic, or immunomodulation properties. Statins have been studied in other areas such as in treatment of portal hypertension, prevention of hepatocellular carcinoma, and/or protection against ischemia/reperfusion injury.

Summary Approved indications for statins in patients with cirrhosis are those of the general population, including dyslipidemia and increased cardiovascular risk. Compensated cirrhosis is not a contraindication. In patients with decompensated cirrhosis, statins should be prescribed with extreme caution at low doses, and with frequent monitoring of creatinine phosphokinase levels in order to detect adverse events in a timely fashion.

Introduction

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase commonly known as statins are drugs originally developed to treat hypercholesterolemia. However, its use in patients with chronic liver disease has been limited because one of its potential and most feared side effects is hepatotoxicity.

The so-called pleiotropic effects of statins, which are properties independent of their effect on cholesterol levels such as improvement of endothelial dysfunction and antioxidant, antifibrotic, anti-inflammatory, antiproliferative, antiangiogenic, proapoptotic, or immunomodulation effects, have made them the drug class most extensively assessed for drug repurposing, and hepatology is not the exception (Fig. 1) [1–5].

In this review, we will summarize the efficacy and safety of statins in chronic liver diseases and cirrhosis, taking into account both their lipid-lowering and their pleiotropic effects. A summary of the main studies evaluating the use of statins in patients with chronic liver disease can be found in Table 1.

Safety of Statins in Patients with Liver Disease

Myositis and hepatotoxicity are two of the most well-known side effects attributed to statins. The most common liver adverse event with their use consists of an asymptomatic and non-clinically significant elevation of the aminotransferase levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) in up to 3% of patients [32]. This usually occurs within the first week of their use and tends to be transient even if patients continue with the treatment. This phenomenon is most probably due to an alteration in the permeability of the

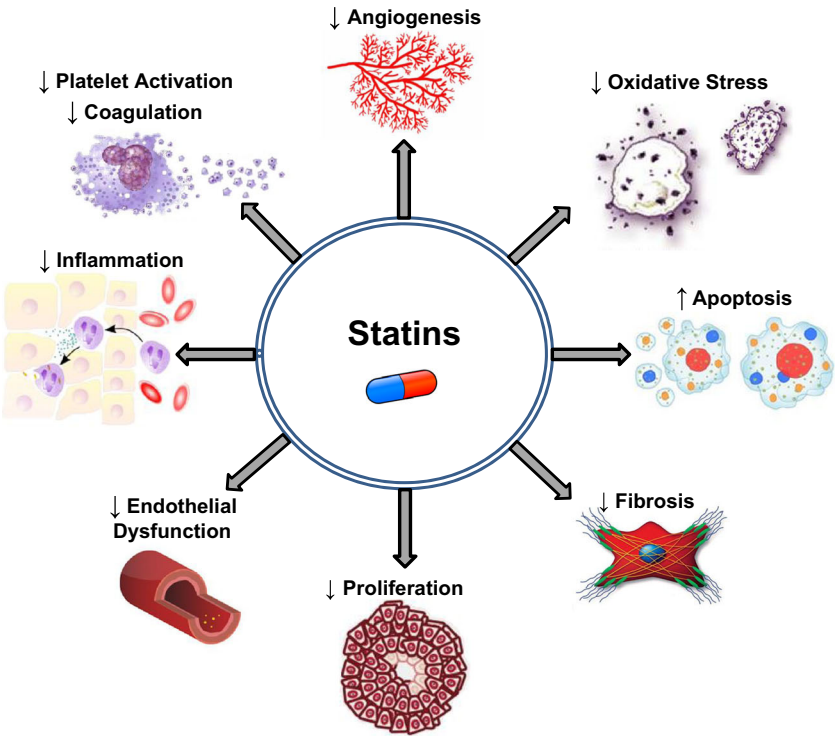

Fig. 1. Pleiotropic effects of statins.

Table 1. Summary of main studies evaluating the use of statins in patients with chronic liver disease

	Author/year	Description	Number	Main findings	Safety concerns
Portal hypertension	Abraldes 2016 [6••]	RCT secondary prophylaxis	69 simvastatin 78 placebo	No effect in rebleeding Better survival in Child A/B patients	2 patients with decompensated cirrhosis developed rhabdomyolysis
	Zafra 2004 [7]	Protocol 1: B&A, open label Protocol 2: RCT	Protocol 1: 13 simvastatin Protocol 2: 9 simvastatin, 8 placebo	Reduction in intrahepatic resistance Increased hepatosplenic output of nitric oxide	NA
	Abraldes 2009 [8]	RCT	28 simvastatin 27 placebo	Significantly reduced HVPG and improved liver perfusion Benefit is additive to that of NSBBs	Side effects were not different compared to placebo
	Pollo-Flores 2015 [9]	RCT	11 simvastatin 13 placebo	Significantly reduced HVPG	Side effects were not different compared to placebo
	Wani 2017 [10]	B&A Open label Primary prophylaxis	38 simvastatin	In 38 non-hemodynamic responders to carvedilol, simvastatin achieved hemodynamic response in 16	1 patient developed myositis
PBC	Del Puppo 2001 [11]	B&A Open label	6 simvastatin	Reduced cholesterol levels	No significant side effects
	Kurihara 1993 [12]	B&A Open label	2 pravastatin	Reduced cholesterol and bile acid levels	N/A
	Ritzel 2002 [13]	B&A Open label	6 simvastatin	Reduced cholesterol levels	Not significant
	Stojakovic 2010 [14]	B&A Open label	19 atorvastatin	Reduced cholesterol levels	2 patients withdrawn for elevation of CPK. One of them had baseline abnormalities in CPK and the other one had Sjögren-associated myositis

Table 1. (continued)

	Author/year	Description	Number	Main findings	Safety concerns
	Stojakovic 2007 [15]	B&A Open label	15 atorvastatin	In 15 non-responders, UDCA did not improve biochemical response but it did reduce cholesterol levels	3 patients developed significant elevation in ALT
NAFLD	Eslami 2013 [16]	Review (2 RCT)	RCT 1 10 simvastatin 6 placebo RCT 2 63 atorvastatin 62 fenofibrate 61 atorvastatin and fenofibrate	High risk of bias, more studies needed	1 patient in the atorvastatin group developed significant elevation in ALT 1 patient in the atorvastatin group and 2 in the atorvastatin /fenofibrate group developed significant elevation in CPK
	Kargiotis 2015 [17••]	B&A Open label	20 rosuvastatin	Resolution of NASH in 19 patients	No significant side effects
HCV	Simon 2016 [18]	Retrospective analysis of cohort	9135 (4165 statin users) - 2305 simvastatin - 944 atorvastatin - 609 pravastatin	Associated with reduced risk of HCC and fibrosis progression	N/A
	Mohanty 2016 [19••]	Retrospective analysis of cohort of patients with cirrhosis Propensity score matching	40,512 (2802 statin users)	Reduced risk of decompensation and death	N/A
	Harrison 2010 [20]	Retrospective analysis of patients treated with PEG/RBV	3070 (66 statin users) - 44% atorvastatin - 17% pravastatin - 15% simvastatin	Associated with SVR	No significant differences in adverse events were seen. However, there was a significantly higher number

Table 1. (continued)

	Author/year	Description	Number	Main findings	Safety concerns
					of dose modifications of RBV among the statin users
	Manzano-Robledo 2015 [21]	Meta-analysis of patients treated with PEG/RBV/PI (33 studies)	10,525 patients	Associated with SVR	N/A
	Chang 2017 [22]	Retrospective analysis of cohort of patients with cirrhosis Propensity score matching	298 patients (146 statin users)	Associated with decreased risk of decompensation	N/A
HBV	Chang 2017 [22]	Retrospective analysis of cohort of patients with cirrhosis Propensity score matching	605 (313 statin users)	Associated with decreased risk of decompensation and death	N/A
	Chen 2015 [23]	Retrospective analysis of cohort of patients with HBV Propensity score matching	71,824 (8861 statin users)	Reduced risk of HCC and non-liver cancers	N/A
	Hsiang 2015 [24]	Retrospective analysis of cohort of patients with HBV Propensity score matching	53,513 (1176 statin users) - 997 simvastatin/atorvastatin - 179 rosuvastatin/fluvastatin	Reduced risk of HCC	N/A
	Huang 2016 [25]	Retrospective analysis of cohort of patients with HBV Propensity score matching	238,346 (22,544 statin users)	Reduced risk of progression to cirrhosis and decompensation	N/A

Table 1. (continued)

	Author/year	Description	Number	Main findings	Safety concerns
HCC	Butt 2015 [26]	Meta-analysis of patients treated with PEG/RBV	7248 (3334 statin users)	Associated with reduced risk of HCC, lower fibrosis progression, and higher SVR	N/A
	Lai 2013 [27]	Case control	3480 cases 13,920 controls	Simvastatin, lovastatin, atorvastatin associated with reduced risk of HCC	N/A
	Singh 2013 [28]	Meta-analysis (10 studies)	1,459,417 patients 4298 cases	37% risk reduction of HCC Significant heterogeneity	N/A
Ischemic hepatitis	Drolz 2014 [29]	Cohort of patients admitted to ICU	851 (155 statin users) -45% atorvastatin - 43% simvastatin	Reduced risk of ischemic hepatitis	No significant adverse effects
Compensated cirrhosis	Kumar 2014 [30]	Retrospective analysis	243 (81 statin users) - 49% simvastatin - 30% atorvastatin	Better survival and reduced risk of decompensation	N/A
	Motzkus-Feagans 2013 [31]	Retrospective analysis Propensity score matching	19,379 (2468 statin users) - 90% simvastatin - 9.4% lovastatin	Reduced risk of infectious-related hospitalizations	N/A

B&A before and after study design, *CPK* creatinine phosphokinase, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HVPG* hepatic venous pressure gradient, *ICU* intensive care unit, *N/A* not available, *NAFLD* non-alcoholic fatty liver disease, *NASH* non-alcoholic steatohepatitis, *NSBB* non-selective beta blocker, *PBC* primary biliary cholangitis, *PEG/RBV* peginterferon/ribavirin, *RCT* randomized controlled trial, *SVR* sustained viral response, *UDCA* ursodeoxycholic acid

hepatocyte membrane that leads to a leak of liver enzymes, rather than to damage to the hepatocyte per se. This is supported by the fact that liver biopsies done in these patients do not show significant abnormalities. Only 3% or less of patients will have a persistent elevation of aminotransferases [32, 33].

In a study from the Drug-Induced Liver Injury Network (DILIN) of the USA, drug-induced significant toxicity [ALT or AST > 5 times the upper limit of normal (ULN) and/or alkaline phosphatase > 2 times ULN], statins were implicated in 1.8% of cases of drug-induced liver injury [34]. Importantly, four patients with statin-induced injury developed acute liver failure, of which one patient died, although this patient had alcohol-induced cirrhosis.

In another study of 133 patients with acute liver failure, statins were deemed responsible of 4.5% of cases [35]. The risk of hepatotoxicity related to statins is variable, but it has been estimated in 1 of every 3700 to 11,000 users. The mechanism of liver toxicity is an idiosyncratic reaction, which most commonly occurs during the first months of use, but the latency has been reported of up to 10 years in some cases. Liver toxicity seems to be a class effect, but the statins most commonly implicated are atorvastatin, simvastatin, and fluvastatin [36]. In the case of atorvastatin, the risk of developing significant elevation of aminotransferases (> 3 ULN) is 0.3%. However, in patients receiving high doses (≥ 80 mg), this can increase up to 2.3%. As mentioned above, most of the elevations in liver enzymes are transient, asymptomatic, and not clinically relevant. Nonetheless, atorvastatin can be implicated in clinically significant liver toxicity in 1 of 3000 to 5000 users, usually showing a cholestatic or mixed pattern in the liver biochemistry tests, though a hepatocellular pattern can also be seen in some cases. There are case reports of atorvastatin-induced autoimmune hepatitis [37].

In the case of simvastatin, the most common liver pattern of liver injury is hepatocellular. Significant elevation of aminotransferase levels is present in 1% of cases of long-term users, though clinically significant hepatotoxicity is uncommon. There are also case reports of simvastatin-induced acute liver failure or autoimmune hepatitis [38].

Patients with baseline abnormalities in liver biochemistry tests, for example because of non-alcoholic fatty liver disease (NAFLD) or chronic hepatitis C virus (HCV) infection, including patients with compensated cirrhosis, do not have a higher risk of statin-induced liver injury when compared to the general population. Therefore, if a patient with a chronic liver disease or with preexistent alterations in liver biochemistry tests has an indication for statins (e.g., hypercholesterolemia), there is no reason to refrain prescribing them [36, 39–41].

Current recommendations of the Food and Drug Administration consist in testing baseline AST and ALT when initiating statins, but it is no longer recommended to monitor them periodically, unless there is an additional clinical indication for monitoring AST/ALT levels, as this strategy has not shown to be effective in detecting or preventing liver injury [42••].

Decompensated cirrhosis is a different scenario, it seems that as liver function worsens, there is a reduced expression of the solute carrier organic anion transporter family member 1B (SLCO1B) in the hepatocytes, a membrane transporter that modulates the uptake of statins. This leads to an increase in statin serum concentrations with the subsequent increase in the risk of adverse events, including myopathy and hepatotoxicity [43, 44]. In the Bleeding Prevention with Simvastatin (BLEPS) study, a randomized clinical trial (RCT) that assessed

simvastatin as a variceal bleeding secondary prophylaxis strategy, 3% (2/69) of the patients that received simvastatin (40 mg) developed rhabdomyolysis, which is a much higher frequency than that reported in general population. Of note, the two patients that developed this complication had decompensated cirrhosis with a bilirubin > 5 mg/dl [6••]. Additionally, in this same study, the use of simvastatin was associated with increased survival in patients with class Child-Pugh A/B cirrhosis, but not in Child-Pugh C [6••, 42••].

Statins and Treatment of Portal Hypertension

Only 40% of the patients that are started on non-selective beta blockers (NSBBs) for primary prophylaxis of variceal bleeding due to portal hypertension achieve a hemodynamic response. In the case of secondary prophylaxis, the 2-year rebleeding rate with standard therapy (NSBBs plus endoscopic banding) is of 30%; therefore, there is room for improvement in the management of these patients. Treatment of portal hypertension should aim at improving all elements implicated in its physiopathology: liver injury, liver function, fibrogenesis, increased intrahepatic vascular resistance, and the splanchnic vasodilation. Statins are an attractive therapeutic alternative because they are capable of modifying the intrahepatic vascular resistance, and studies in experimental models suggest that they can also impact the fibrogenesis [45].

Based on positive results of the effects of simvastatin in portal hypertension in animal models [5, 46], Zafra et al., a proof of concept study, demonstrated that simvastatin administration decreased hepatic vascular resistance, likely through an increase in liver nitric oxide production [7]. In a subsequent RCT, 55 patients with cirrhosis were randomized to receive simvastatin or placebo and had baseline hepatic venous pressure gradient (HVPG) measurement after one month of treatment [8]. Simvastatin induced a reduction of 8.3% in the HVPG. Importantly, this benefit was an additive to that of the NSBBs. Patients that were on NSBBs had a reduction of 11% compared to 5.9% of those that were not on NSBBs. In addition to this, simvastatin improved liver perfusion and function as shown by an improvement in the indocyanine green clearance test. In a similar three-month RCT of 34 patients with cirrhosis randomized to simvastatin or placebo, patients on simvastatin achieved a clinically relevant reduction of the HVPG (reduction of ≥ 20% or to < 12 mmHg) in 55% of patients [9].

Finally, in a prospective study of 100 patients with cirrhosis, esophageal varices, and an HVPG > 12 mmHg, the efficacy of simvastatin was evaluated in those without hemodynamic response to carvedilol (NSBB β1, β2, and an alpha adrenergic receptor blocker α1). Of the 100 patients, 38 had no hemodynamic response and were started on simvastatin (40 mg qd). Hemodynamic response was achieved in 16 patients [10]. This result is particularly interesting because it would mean that with the combination of carvedilol/simvastatin, 80% of patients could achieve hemodynamic response. Nonetheless, a major drawback of the study is that it did not include a control group.

There is only one RCT that has evaluated the effects of statins in patients with cirrhosis assessing clinical endpoints. This was a phase III RCT with a 2-year follow-up in which 147 patients were randomized to simvastatin or placebo after an episode of acute variceal bleeding. All patients received standard secondary prophylaxis (banding and NSBBs). The primary endpoint was a

composite variable of rebleeding and/or death. Simvastatin did not improve the rate of rebleeding. However, there was a significant improvement in survival with simvastatin, mainly related to a decrease in bleeding and sepsis-related death [6••]. Due to the fact that mortality was not the primary endpoint of this study, these results need further validation in new RCTs with clinical endpoints.

Statins for the Treatment of Dyslipidemia in Patients with Chronic Liver Disease

Patients with cirrhosis, as any other patient, can have hyperlipidemia and increased cardiovascular risk, making them candidates to pharmacological treatment with statins. As a matter of fact, patients with NAFLD and HCV have an increased risk of premature atherosclerosis, which is independent of the traditional cardiovascular risk factors [47]. Also, up to 27% of patients with end-stage liver disease listed for liver transplant have significant coronary artery disease [48]. It is also worth mentioning that patients with cholestatic liver diseases have a high prevalence of hypercholesterolemia. In this section, we will review the evidence regarding the safety and utility of statins in these conditions [49].

Chronic Cholestatic Liver Diseases

Despite the fact that there is a high prevalence of hypercholesterolemia in patients with chronic cholestatic diseases, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), treatment with statins is controversial due to the fact that these patients do not seem to have an increased cardiovascular risk when compared to the general population [49]. Pharmacological treatment is usually recommended only in the presence of additional cardiovascular risk factors such as obesity, smoking, hypertension, diabetes, or family history of premature cardiovascular disease [49]. There is evidence from non-controlled studies and with a small number of patients that suggests statins are safe and effective for the treatment of hyperlipidemia in patients with PBC, which can have a prevalence of hypercholesterolemia of up to 58%. Therefore, these patients should be started on statins whenever there is a clinical indication [11–15, 50].

Non-alcoholic Fatty Liver Disease

Patients with NAFLD have an increased frequency of the different components of the metabolic syndrome, including dyslipidemia of in 20 to 80% of patients. As in other clinical scenarios, abnormal liver biochemistry tests should not preclude the prescription of statins in these patients, as the most common cause of death in this group of patients is cardiovascular disease [51].

The use of statins as a therapeutic strategy for NAFLD, either steatosis or steatohepatitis, is not supported with strong evidence. In a systematic review of the Cochrane Collaboration of statins in NAFLD, after applying inclusion criteria for the selection of the studies, it was found that only two were eligible, both with high risk of bias and only one of them with histopathological outcomes [16]. As a result, no meta-analysis or firm conclusions could be made.

A more recent study evaluated 20 patients with biopsy-proven steatohepatitis that received rosuvastatin for 12 months. At the end of follow-up, a new liver biopsy was performed, and there was resolution of steatohepatitis in 19 of the 20 patients. Unfortunately, there was no control group, and this greatly limits the interpretation of the results [17••]. There is a need for further RCTs assessing the role of statins in NAFLD.

Statins in Chronic Hepatitis

Chronic HCV Infection

There is biologic plausibility behind the study of statins in chronic HCV. The HCV circulates as a lipoviral particle, and similar to apolipoproteins, it contains ApoE and ApoB on its surface, promoting its entry to the liver cells after binding to the low-density lipoprotein (LDL) cholesterol and to the scavenger receptor class B member 1 (SRB1). In order for the HCV to achieve a successful replication, it has to upregulate the host transcription of genes implicated in lipid metabolism. Consequently, the inhibition of cholesterol synthesis could have therapeutic implications by interfering with viral replication [52, 53].

In vitro studies have shown that statins have anti-HCV activity, and among the different types of statins, the one with the most potent antiviral activity seems to be fluvastatin, followed by atorvastatin and simvastatin [54]. Based on this assumption, Sheridan et al. [55] randomized 60 patients with HCV to fluvastatin and/or omega 3 fatty acids or no active treatment and assessed the impact of these strategies on the viral load. The study was negative and there was no association between these therapeutic strategies and changes in viremia after three months of treatment. Similar results were found in the study by Simon et al. [56] that evaluated 543 patients with chronic HCV, of whom 29 were chronic users of statins.

Information of the effects of statins on clinical outcomes in patients with chronic HCV comes from observational studies. In a retrospective study of 7248 patients with chronic HCV that received antiviral treatment and had a minimum follow-up of 2 years, a significant association was found between the use of statins (3347 patients of the sample) and a decrease in fibrosis progression. Moreover, the use of statins was associated with the possibility of achieving sustained viral response (SVR) and with a decreased risk of developing hepatocellular carcinoma (HCC). It is worth mentioning that there were significant baseline differences between the groups, so despite the fact that the authors adjusted for potential confounders with Cox proportional hazard models, the results should be interpreted with caution, as these were not RCTs [26]. Likewise, in a study of 9135 patients with chronic HCV, statins were associated with a reduced risk of fibrosis progression, and of HCC [18]. In another study of 2747 patients with HCV-induced cirrhosis that used a propensity score matching strategy to compensate for the potential confounding by indication bias, a significant association was found between the use of statins and a reduced risk of death and liver decompensation [19••]. A recent study in Asian population that included 298 patients with HCV-related cirrhosis also found that statins were associated with a decreased liver decompensation rate [22]. Moreover, retrospective observational studies from the era of the HCV treatment with interferon, ribavirin, and boceprevir found significant association between

statins and the rates of SVR [20, 21]. The relevance of this information in the era of direct acting antivirals with SVR higher than 90% is uncertain, and in fact, it is possible that the interaction between the new treatments and statins may increase the concentration of the latter, with the potential of risk of adverse events [53].

Chronic HBV Infection

There is less evidence of the use of statins in patients with chronic HBV. Even though some in vitro studies suggested an anti-HBV effect [57], this has not been translated in clinical practice. However, large cohort studies in Asian population have shown an association between statins and a decreased risk of HCC, both in patients with and without cirrhosis. In addition to this, they also seem to decrease the rate of progression to cirrhosis, and in patients with cirrhosis, they have been associated with a reduced risk of liver decompensation and death [22–25, 58].

Statins and Prevention of HCC

The pleiotropic effects of statins, such as their antiangiogenic properties, make them an attractive option for cancer prevention. In terms of HCC, a recent meta-analysis reported a 37% risk reduction of developing HCC in patients taking statins, though there was significant heterogeneity between the studies. Of note, the statistical association was lost in a sub-analysis that included only RCT and was free of significant heterogeneity [28]. As mentioned above, this association has also been studied in patients with chronic HCV and HBV [22–24, 26], in whom a dose-response relationship was suggested. One study in Asian populations not included in the previous meta-analysis also proposed this association [27]. In order to confirm this association, a long-term follow-up RCT with an adequate number of patients would be needed.

Other Potential Benefits of Statins in Patients with Liver Disease

Data from observational studies suggest that statins could modify the natural history of cirrhosis. In a retrospective analysis of 243 patients with cirrhosis (70% child A), whom 81 were on statins, there was a significant association between the use of statins and improved survival, and decreased risk of liver decompensation [30], essentially replicating the findings of a previous study in patients with chronic HCV [19••]. Moreover, a recent meta-analysis including most of the aforementioned studies showed a significant association between statins and a lower risk of liver decompensation and death in patients with cirrhosis [59••].

Statins have also been associated with a decreased risk of incident infections. Statins are capable of fostering the activity of phagocytes [60], and in an animal model, simvastatin was able to attenuate the liver endothelial dysfunction induced by endotoxemia [61]. In the same line, a retrospective study of patients with cirrhosis that used propensity score matching reported an inverse association between statins and infectious-related hospitalizations. Importantly, when comparing the results of patients on statins with

those taking other lipid-lowering agents, no differences were found, so it cannot be ruled out that the findings in fact are due to features associated with patients that receive treatment for hyperlipidemia [31]. Moreover, in the BLEPS study, the association between simvastatin and decreased mortality was mainly due to a reduction in infections and bleeding-related deaths [6••].

Animal models suggest that statins could blunt the ischemia-reperfusion-induced liver injury in grafts with steatosis in the context of liver transplantation [62], and they could have a role in the treatment of hepatopulmonary syndrome [63]. In one experimental study in rats that underwent hemorrhage shock and subsequent resuscitation, simvastatin was capable of reducing liver necrosis and was associated with improved survival. The rationale underlying this finding is that part of the liver injury is promoted by a dysregulation in the production of nitric oxide that can be overcome by statins [64]. Likewise, in a cirrhosis model in rats, pretreatment with simvastatin blunted the liver injury after hemorrhage—resuscitation [65]. Moreover, a retrospective analysis of 851 patients admitted to an intensive care unit found that previous use of statins was a protective factor for ischemic hepatitis, further supporting the evidence described in animal models [29].

There are also experimental models that have assessed the use of statins to improve liver fibrosis with encouraging results [66]. These animal studies should be replicated in humans, and this could be the ground basis for the design RCTs with clinical endpoints in specific subpopulations.

Conclusions

At present, the only approved indications for statins in patients with cirrhosis are those of the general population (i.e., dyslipidemia, increased cardiovascular risk). There is a special need for new RCT with an adequate number of patients to demonstrate that the pleiotropic effects of statins can modify clinically significant endpoints in patients with cirrhosis, since the current evidence comes mostly from observational studies or clinical trials with a limited number of patients [67].

The presence of abnormal liver biochemistry tests, chronic liver disease, and compensated cirrhosis should not be seen as contraindication for the use of statins, if the classical indications are present. However, in patients with decompensated cirrhosis, statins should be prescribed with extreme caution at low doses, and with frequent monitoring of creatinine phosphokinase levels in order to detect adverse events in a timely fashion.

Compliance with Ethical Standards

Conflict of Interest

Carlos Moctezuma-Velázquez declares that he has no conflict of interest. Juan Abraldes declares that he has no conflict of interest. Aldo Montano-Loza declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Prospective study that showed a lower mortality in patients that received statins.

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This article shows that further investigation is needed regarding the role of statins in the treatment of NAFLD.

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Specific recommendations of a panel of experts about the liver safety of statins; the strength of the recommendations and quality of evidence are given.

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