Statins: Old drugs as new therapy for liver diseases?

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Summary

In addition to lowering cholesterol levels, statins have pleiotropic effects, particularly anti-inflammatory, antiangiogenic, and antifibrotic, that may be beneficial in some chronic inflammatory conditions. Statins have only recently been investigated as a potential treatment option in chronic liver diseases because of concerns related to their safety in patients with impaired liver function. A number of experimental studies in animal models of liver diseases have shown that statins decrease hepatic inflammation, fibrogenesis and portal pressure. In addition, retrospective cohort studies in large populations of patients with cirrhosis and pre-cirrhotic conditions have shown that treatment with statins, with the purpose of decreasing high cholesterol levels, was associated with a reduced risk of disease progression, hepatic decompensation, hepatocellular carcinoma development, and death. These beneficial effects persisted after adjustment for disease severity and other potential confounders. Finally, a few randomised controlled trials have shown that treatment with simvastatin decreases portal pressure (two studies) and mortality (one study). Statin treatment was generally well tolerated but a few patients developed severe side effects, particularly rhabdomyolysis. Despite these promising beneficial effects, further randomised controlled trials in large series of patients with hard clinical endpoints should be performed before statins can be recommended for use in clinical practice.

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Key point

Statins have shown potential beneficial effects in chronic inflammatory diseases, including chronic lung diseases, neurological disorders and chronic kidney disease.

Introduction

Statins were discovered as a by-product in the research for new antimicrobial agents.[1] They represent a heterogeneous group of molecules that inhibit the activity of hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, a key enzyme in the synthesis of cholesterol. Thus, statins are used for the management of dyslipidaemia, worldwide.[2] Besides their lipid-lowering property, statins also exhibit multiple pleiotropic effects such as antioxidative, antiproliferative and anti-inflammatory properties, as well as the capacity to improve endothelial function and to stimulate neoangiogenesis.[3] It is not known to what extent these effects are related to the primary effect of these drugs, nevertheless, several studies have demonstrated that statins significantly reduce the risk of cardiovascular morbidity and mortality.[4] As a consequence, statins are among the most prescribed class of medications worldwide and an increasing number of patients have received statins as primary or secondary prophylaxis for cardiovascular events in the last decades in all developed countries.[5] It is well known that statins can cause elevations in serum aspartate and alanine aminotransferase levels. Thus, there is still some residual concern among primary care physicians in prescribing statins to patients with underlying liver disease, since some of them still think that these patients may be at increased risk of hepatotoxicity.[6] However, liver damage due to statins is extremely rare and the exact mechanism by which they cause aspartate and alanine aminotransferase elevation is still uncertain. An elevation of liver enzymes >3 times the upper limit of normal has been observed in <1% of treated patients.[7,8] Paradoxically, several studies have recently shown that statins might offer clinical benefits in the setting of liver disease, including in non-alcoholic fatty liver disease (NAFLD), cholestatic liver diseases, and cirrhosis. In particular, this class of drugs was shown to ameliorate functional alterations and liver histology in patients with NAFLD, while also reducing their risk of cardiovascular events.[9] In addition, the use of statins in patients with cirrhosis has been shown to reduce portal hypertension, as estimated by a significant decrease in hepatic venous pressure gradient (HVPG), and reducing the risk of decompensation and death.[10] Thus, despite statins being considered 'forbidden-drugs' in patients with increased liver enzymes for several years, nowadays there is a growing interest in their potential benefits in patients with liver diseases.

Rationale for the use of statins in chronic disorders

As mentioned, beyond their role in lipid lowering and consequent application in patients with known cardiovascular risks, statins have pleiotropic effects that target key processes in the pathophysiology of many chronic diseases. Firstly, they

act on inflammation by: i) decreasing leukocyte adhesion to endothelia and epithelial cells by inhibiting expression and binding of LFA-1 and ICAM-1; ii) decreasing the production of NF-kB and hence the release of pro-inflammatory cytokines such as TNFα and IL-6; and iii) blocking of prenylation of key proteins required for the formation of lipid rafts and immune cell activation and growth.[11,12] Statins also decrease the level of oxidative stress by reducing the levels and oxidation of low density lipoprotein, in addition to reducing inducible nitric oxide (iNOS) production, and thereby impacting on nitrosative stress.[13,14] Moreover, statins promote the mobilization and activation of endothelial progenitor cells, important for angiogenesis and regenerative capacity.[15] The ability of statins to decrease inflammation and promote healing has been shown to be beneficial in many chronic diseases, ranging from obstructive airways disease to neurodegenerative disorders, examples of which are elaborated on.

Chronic lung diseases

The pathophysiology of chronic obstructive lung disease involves i) enlargement of distal airways and destruction of their walls in the absence of fibrosis (emphysema) and ii) a remodelling and narrowing of small airways predominantly in smokers, whereby fibrosis, mucus hypersecretion and metaplasia, increase airway wall thickness.[16] In these scenarios, there is a chronic stimulation of the innate immune system, with migration of immune cells to the lungs, resulting in the generation of pro-oxidants and the release of inflammatory cytokines.[17] Indeed, patients with increased inflammatory indices such as C-reactive protein (CRP) are at increased risk of chronic obstructive pulmonary disease (COPD) exacerbations and more rapid decline in lung function.[18]

As previously described, many of these pathological processes lend themselves to targeting by statins. A large series of 14,000 patients with COPD from Taiwan showed that those taking statins had decreased hospitalisations and a 30% reduction in COPD exacerbations.[19] Whilst a reduction in mortality has not been universally shown in prospective studies of patients with COPD on statins vs. those not on treatment,[20] several cohort based retrospective studies have shown a reduction in all-cause mortality ranging from 21–35%.[21,22] However, it is important to note that further critique of controlled trial data suggests that these retrospective studies failed to exclude patients with cardiovascular indications for starting statin therapy. Thus, any perceived benefit was likely from improved clinical outcomes in patients enrolled with cardiovascular disease or risk (elevated baseline cholesterol or CRP).[23,24] These studies resulted in the suggestion, in the GOLD guidelines for management of COPD, that statin therapy should not be recommended to reduce exacerbations of COPD in patients with no risk factors for cardiovascular disease [GOLD 2017 http://www.goldcopd.org].

Neurological disorders

The benefits of lipid lowering after ischaemic cerebrovascular events are well established, but given the anti-inflammatory effects and vascular remodelling actions of statins, other neurological conditions have also been explored. One such state is chronic subdural haematoma, where there is impaired angiogenesis in the neomembrane of the haematoma and also localised inflammation.[25] Atorvastatin has been shown to improve angiogenesis and increase the levels of circulating endothelial progenitor cells through activation of endothelial nitric oxide synthase (eNOS) and the threonine kinase Akt, in preclinical models of chronic subdural haematoma.[26] Moreover, statins facilitate the migration of endothelial progenitor cells by blocking inhibitory miR-221 and miR-222, as has been studied in cultured human endothelial cells.[27] Furthermore, the anti-inflammatory effect of statins has been shown to promote functional recovery in rats with induced subdural haematoma.[28] In addition, a meta-analysis of randomised controlled trials (RCTs) of statin therapy suggested that statins promote a significant reduction in vascular endothelial growth factor (VEGF) level.[29] VEGF is believed to be in high concentrations in haematoma fluid and increases its volume; VEGF inhibition with statins might be beneficial in managing the early impact of chronic subdural haematomas. However, a detailed clinical evaluation of statin therapy in patients with chronic subdural haematomas is still awaited.

Inflammatory cascades, oxidant stress, microglial activation and the aggregation of α-synuclein, all contribute to the development of progressive and debilitating neurodegenerative disorders, such as Parkinson's disease (PD). These processes are all positively impacted upon by statins.[30] Simvastatin is known to effectively cross the blood brain barrier and enter the substantia nigra, decreasing the activation of NF-κB and pro-inflammatory cascades, and restoring locomotor function in a murine model of PD.[31,32]

Similarly, pitavastatin and atorvastatin have been shown to protect against senile plaque formation and reduce microglial activation in a rodent model of Alzheimer's disease.[33] These findings also extend to models of cerebral injury after cardio-pulmonary bypass, where neuronal loss and memory impairment are prevented by simvastatin therapy.[34] In addition to these preclinical results that support the use of statins in neurological disorders, retrospective reviews of patients on lipid-lowering therapy have suggested that statin therapy improves global cognition in patients with PD,[35] or delays the onset of PD.[36] A meta-analysis of over three million individuals with over 21,000 incident cases of PD, suggested a lower risk of PD in those patients on statin therapy.[37]

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Chronic kidney disease

Whilst application of statins to patients with kidney dysfunction secondary to diabetes mellitus is standard practice, and has been suggested to reduce the risk of diabetes complications, statins have also been shown to decrease the risk of vascular events in patients with advanced chronic kidney disease (CKD). The SHARP study showed patients treated with simvastatin plus ezetimibe had significantly fewer atherosclerotic events (17%), especially non-haemorrhagic stroke, over a median follow-up of just under five years, compared to patients not receiving lipid-lowering therapy.[38] In addition, a further study in over 14,000 patients with predialysis advanced CKD, showed reduced all-cause mortality and reduced risk of needing future dialysis in patients treated with statins compared to those not treated.[39] Of note, in this study, there was no apparent reduction in risk of ischaemic stroke or intracranial haemorrhage.

The aforementioned examples highlight the potential benefits of statin therapy in chronic diseases, arguing for the use of statins beyond their traditional cardiovascular applications. Statins may be particularly relevant in cases where there is a need to lower systemic inflammation, enhance vascular regeneration and reduce oxidative stress.

Statins in liver diseases

Studies in experimental liver diseases

Effects of statins on steatosis

Traditionally, statins have been used in patients with metabolic syndrome (MS) and dyslipidaemia, since statins decrease LDL cholesterol levels in serum. Animals and patients with MS usually display NAFLD and its progressive form of non-alcoholic steatohepatitis (NASH).[40] By decreasing LDL and activating sterol regulatory element-binding proteins (SREBPs), peroxisome proliferator-activated receptor alpha (PPARα) and β-oxidation, statins may reduce hepatic steatosis.[41] This hepatoprotective effect of statins has already been demonstrated in steatotic livers of animal models of transplantation,[42] but not in a combined genetic and dietary model of NASH.[40,43] Therefore, the beneficial effects of statins in experimental steatosis remain controversial.

Effects of statins on inflammation and fibrosis

Statins have shown anti-inflammatory and antifibrotic effects in experimental models of chronic liver injury. Statins exert anti-inflammatory effects via the inhibition of small GTPase prenylation and the decrease in downstream signalling.[43]

The potential beneficial effects of statins in fibrosis have been assessed in different experimental models of chronic liver injury. In experimental NASH, statins affect the paracrine signalling of hepatocytes on hepatic stellate cells (HSCs),[44] blocking hepatic stellate cell (HSC) activation and fibrogenesis.[43,44]

In a bile duct ligated (BDL) mouse model, the antifibrotic effect of statins seems to be mediated via a reduction in serum bile acid levels, which is at least partly due to activation of pregnane X receptor and PPARα.[45] The antifibrotic effect appears to be marked in early stages of BDL-induced liver injury, while in later stages the aggressiveness of the BDL model overrides the beneficial effects of statins.[46] In this model, fibrogenesis is also attenuated as shown by the levels of collagen fragments as a readout of remodelling during fibrogenesis[47] and by a reduction in HSC activity,[46] most likely due to induction of senescence.[48] Statins may also improve fibrosis by inhibiting the RhoA/Rho-kinase pathway in HSCs and by restoring the sinusoidal endothelial function through KLF2 induction.[49]

In other animal models, such as angiotensin-II induced liver fibrosis, statins have also been shown to decrease fibrosis by reducing inflammatory activity.[50] Overall, statins improve fibrosis progression in different models of chronic liver injury.

Effects of statins on portal hypertension

All aetiologies of liver disease share a common end-stage, which is characterised by profound liver remodelling and portal hypertension. An additional dynamic component of increased intrahepatic resistance is an imbalance in the vascular tone-regulating pathways (RhoA/Rho-kinase and nitric oxide [NO]) showing a shift towards vasoconstriction. All these pathways may be modulated by statins.[49,51–53] While statins inhibit translocation of RhoA and, thus, the activity of Rho-kinase,[52] they improve endothelial dysfunction by increasing the activity of eNOS and the availability of NO.[52,54] As mentioned before, by modulating Rho-kinase activity and also KLF2 expression statins also show anti-fibrotic properties that may contribute to reducing portal hypertension.[53] Statins can thereby modulate the dynamic as well as the structural (fibrosis) components of chronic liver diseases and be potentially useful in the management of cirrhosis with portal hypertension. The possible intracellular mechanisms of statins in liver cells are shown (Fig. 1).

Effects of statins on oncogenesis

Statins might also exert antineoplastic properties. Besides inhibition of cell proliferation *in vitro*, statins might also induce apoptosis of hepatoma cells and inhibit intrahepatic angiogenesis.[55] Interestingly, the anti-angiogenic effect is dependent on the context of chronic liver disease; while in experimental cirrhosis statins have beneficial effects, in experimental non-cirrhotic portal hypertension statins increase intrahepatic angiogenesis and aggravate portal hypertension.[56] Reduced proliferation might be due to interference with KRAS and prevention of p21 and 27 breakdown in malignant cells followed by induction of

Key point

Studies in animal models of liver diseases have shown that statins reduce liver fibrosis, improve endothelial dysfunction and decrease portal pressure.

cell cycle arrest.[57,58] Specific interference with integrins and Rho-kinase, which are expressed at the cell membrane, have been shown to reduce proliferation as well as tumour cell adhesion in an *in vitro* model of hepatocellular carcinoma.[59]

Studies in human liver diseases

There is limited information available on the effects of statins in patients with liver diseases. Earlier studies were aimed at assessing the safety of statins because of the potential concern that liver disease could increase the frequency and/or severity of hepatic injury related to statins and did not focus on the possible beneficial effects of these drugs.[59–61] Nevertheless, in recent years a number of studies have assessed the potentially beneficial anti-inflammatory and antifibrotic actions of statins in the course of chronic liver injury in patients. These studies, together with preclinical evidence, deliver the rationale for the use of statins in chronic liver diseases.[62] In the following two sub-sections we focus on these studies, separating our analysis into pre-cirrhotic conditions and cirrhosis.

Effects in patients with pre-cirrhotic conditions

The effects of statins have mainly been assessed in patients with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections without cirrhosis. All investigations were performed in retrospective-cohorts, including several thousand patients, in which the evolution of patients treated with statins for hypercholesterolemia was compared with that of patients not treated with statins.[63–65] Unfortunately, no RCTs have been performed. Cohorts were derived mainly from detailed patient databases that contained information about patient outcomes and prescribed drugs, specifically, the Veterans Affairs Administration and the Taiwan's National Health Insurance.[63–65] The outcomes analysed were disease progression, as estimated by the development of cirrhosis or increase in serological markers of fibrosis during follow-up, improved response to interferon-based antiviral therapy, development of hepatocellular carcinoma, and mortality. The strengths of these studies are the large number of patients evaluated and the adjustment for confounding factors. Interestingly, the results of these studies show that statins have a favourable effect on the natural history of HBV and HCV infection by decreasing disease progression to cirrhosis and reducing mortality.[63–65] In one study, statin use also reduced the development of hepatocellular carcinoma.[65] A meta-analysis performed with all studies reported until 2016 concluded that statins may delay the progression of fibrosis and reduce hepatic decompensation and mortality.[66] However, these studies are affected by a number of limitations that reduce the validity of the findings, including their retrospective nature, uncertainty about some characteristics of statin use (dose, duration), and difficulty in assessing some of the endpoints. Therefore, statins cannot be recommended as therapy for pre-cirrhotic conditions until high-quality data derived from RCTs are available.

Surprisingly, there is very limited information on the effects of statins in patients with NAFLD despite the fact that many of these patients have indications for treatment with statins. For many years, there was concern that statins might have deleterious effects in patients with NAFLD, by causing liver injury or increasing liver lipogenesis, at the same time as increasing hepatic LDL receptor expression.[67] Contrary to expectations, two recent studies showed that statins are not only safe in patients with NAFLD but they could also be beneficial by decreasing steatosis and fibrosis, and preventing disease progression.[68,69] However, since this information derives from retrospective cohort studies, prospective studies are needed to confirm these beneficial effects.

Effects in patients with cirrhosis

The effects of statins have also been assessed in patients with cirrhosis. To the best of our knowledge, nine studies have been reported, all of them in recent years: five retrospective cohort studies[70–74] and four RCTs.[75–78] The characteristics and results of these studies are summarised (Table 1). The main aetiologies of cirrhosis in the different studies were HCV or HBV infection and alcohol consumption. Only one study included patients with cirrhosis related to NAFLD.[73] Cohort studies included large numbers of patients (up to 19,379 in the largest study)[74] and were derived from detailed patient databases in which the main endpoints were decompensation of cirrhosis and death in four studies,[70–73] and development of infections in one.[74] Patients treated with statins during follow-up were compared with those not treated with statins and endpoints were adjusted for the most important confounding variables. Simvastatin was the most frequent statin used in all studies. The majority of studies used unmatched analysis together with propensity score matched analysis. Statins consistently reduced the risk of decompensation and death in all studies (hazard ratios ranging from 0.29 to 0.58 and 0.46 to 0.66 for decompensation and death, respectively). In addition, one of the studies showed a reduction in the risk of developing hepatocellular carcinoma.[70]

Three randomised, placebo-controlled, double-blind trials have been reported assessing the effect of simvastatin (40 mg/day for one or three months) or atorvastatin (20 mg/day for one month) on portal pressure, as estimated by HVPG, in a small series of patients with cirrhosis and portal hypertension.[75–77] Most patients were Child-Pugh A and had compensated cirrhosis and very few had Child-Pugh C cirrhosis. Statin therapy was associated with a decrease in portal pressure, as estimated by HVPG, whereas no significant

Key point

In patients with pre-cirrhotic conditions, statins may have beneficial effects by preventing disease progression.

Key point

In patients with cirrhosis, statins have shown potential beneficial effects by decreasing portal hypertension and risk of decompensation and may improve survival.
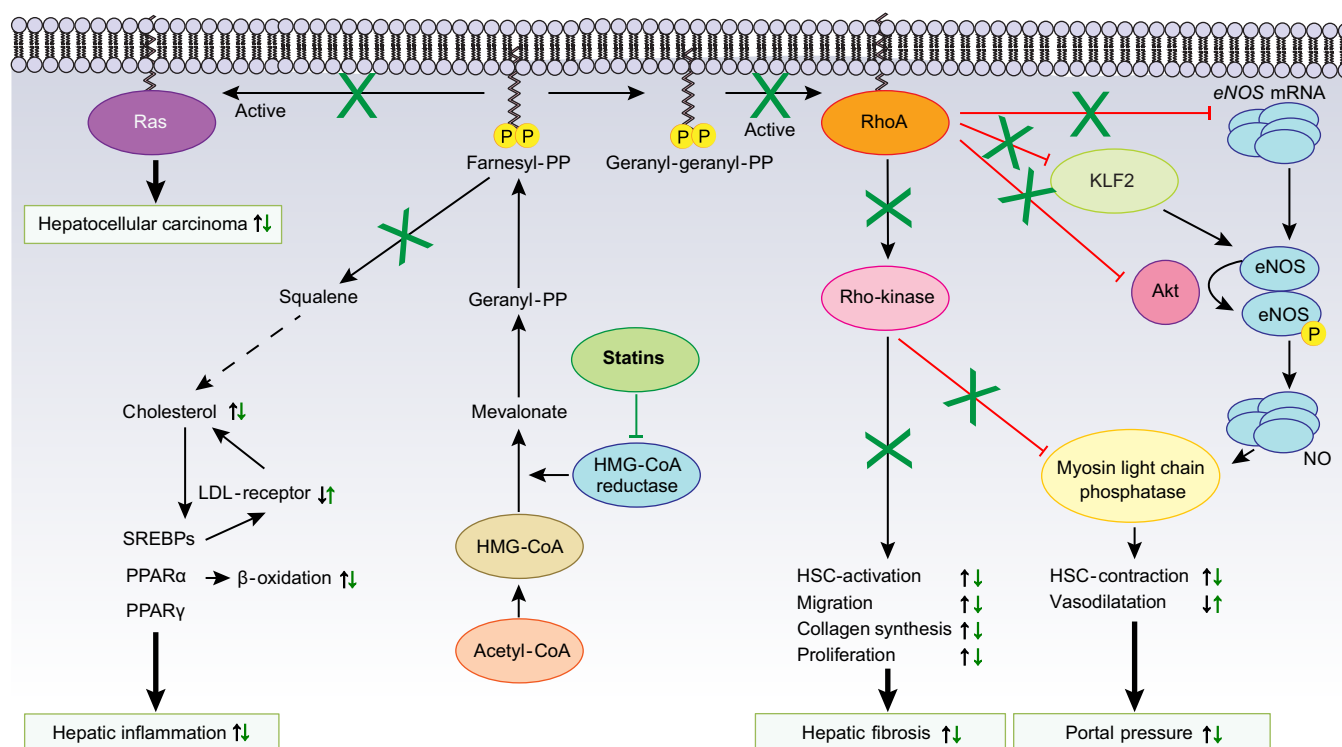
Fig. 1. Pleiotropic effects of statins on small GTPases in the liver. The decrease in activation of small GPTases RhoA and Ras in hepatic stellate cells and liver sinusoidal endothelial cells leads to changes in the subsequent signalling pathways, which results in less fibrogenesis, less hepatic inflammation and lower portal pressure. Additional statins have direct effects on hepatocyte growth and proliferation signals and thereby might abrogate the development of hepatocellular carcinoma.

changes were observed in patients treated with placebo. Moreover, in 32% and 60% of patients treated with simvastatin and in 91% of patients treated with atorvastatin in the three studies, the decrease in HVPG was greater than 20%, indicating a clinically significant reduction in portal pressure in a sizeable proportion of patients treated.

The results of the largest RCT on the effects of simvastatin in cirrhosis were reported very recently.[78] In this study, 158 patients with cirrhosis and portal hypertension were randomised to receive either simvastatin (20 mg/day for the first two weeks followed by 40 mg/day) or placebo during a two-year period. The main endpoint was a composite of rebleeding and death. During a median follow-up of approximately one year, 30 out of 78 (39%) patients in the placebo group and 22 of the 69 (31.9%) patients in the simvastatin group reached the primary endpoint (hazard ratio 0.82; CI 0.47–1.43; $p = 0.42$). Nonetheless, when only death was evaluated, mortality was 22% in the placebo group compared to 9% in the simvastatin group (hazard ratio 0.39; CI 0.15–0.99; $p = 0.03$). The decrease in mortality was mainly due to a reduction in liver-related deaths.

Taken together, the results of cohort studies and RCTs suggest that statins have a beneficial effect on the evolution of cirrhosis by decreasing the risk of decompensation and improving survival. These beneficial effects may be related to the decrease in portal hypertension caused by simvastatin, yet other possibilities cannot be excluded, particularly the possible effects of statins in decreasing systemic and hepatic inflammation. Nevertheless, further RCTs in large series of patients with hard primary endpoints are needed to confirm the beneficial effects of statins on the outcome of patients with cirrhosis. In this regard, a multicentre RCT assessing the effects of the combination of simvastatin and rifaximin for prevention of disease progression and acute-on-chronic liver failure development in patients with decompensated cirrhosis is being conducted in several European countries [https://www.liver-hope-h2020.eu/index_es.html].

Safety of statins in patients with liver diseases
Statins are one of the most prescribed drugs in patients with hyperlipidaemia and for prevention of cardiovascular events, and they are in general well tolerated. In fact, drug-induced liver injury related to statins is extremely rare (<2 cases/1,000.,000 patient-years) and likely idiosyncratic in nature.[79,80] Nevertheless, one side effect of statins that may be of particular concern is muscular toxicity. The spectrum of statin-associated muscle toxicity is considered to include several distinct entities, from myalgia to the most severe and less frequent form, rhabdomyolysis.[81] The risk of muscle adverse events caused by statins seems to be related to statins systemic exposure, so the risk of statin-related muscle toxicity is increased in patients treated with higher doses of statins,[82] and also in patients with polymorphisms in a

Key point

RCTs in large series of patients are needed to confirm safety and beneficial effects of statins in patients with cirrhosis.

Table 1. Retrospective cohort studies and randomised clinical trials of statins in patients with cirrhosis.

Retrospective cohort studies

Study	Patient source	Patient description	Study design	Number of patients	Type of statin	Follow-up period	Endpoints	Results	Comments
F. Chang *Hepatology* 2017	Taiwan National Health Insurance	HBV, HCV and alcohol-related cirrhosis	Retrospective cohort study	1,174 statin users *vs.* 6,453 non-statin users	NA	Approx. median of follow-up of 3 years	Decompensation, death, HCC development	Prevented decompensation aHR 0.39 (0.30–0.50), decreased mortality aHR 0.46 (0.34–0.63), decreased HCC aHR 0.52 (0.35–0.76)	Lower risk of ascites, variceal bleeding and hepatic encephalopathy. Analysis by aetiology in HBV, HCV and alcohol-related cirrhosis. Dose-response relationship
Bang *Aliment Pharmacol Ther* 2017	Danish National Patient Registry	Alcohol-related cirrhosis	Retrospective cohort study	794 statin users *vs.* 4,623 non-users	Simvastatin 79% Atorvastatin 8% Rosuvastatin 6%	Approx. median of follow-up of 4 years	Decompensation, death	Prevented decompensation HR 0.29 (0.24–0.34), decreased mortality HR 0.57 (0.45–0.71)	Adjusted by adhesion to treatment but not for liver function scores. HE not evaluated
Mohanty *Gastroenterology* 2016	US Veterans Health Admin	HCV-related compensated cirrhosis	Retrospective cohort study	1,323 statin users *vs.* 12,522 non-statin users	Simvastatin 85% Lovastatin 10% Pravastatin 3% Rosuvastatin 1% Fluvastatin 1%	Median of 2.5 years for statin users, 1.5 years for non-users	Decompensation, death	Prevented decompensation aHR 0.55 (0.39–0.77), decreased mortality aHR 0.56 (0.46–0.69)	Adjusted for liver tests and scores. Lower risk of ascites and variceal haemorrhage
Kumar *Dig Dis Sci* 2014	Partners Research Patient Data Registry	NASH, alcohol, HBV and HCV-related cirrhosis	Retrospective cohort study	81 statin users *vs.* 162 non-statin users	Simvastatin 49% Atorvastatin 30%	3 years for statin users, 2.5 years for non-statin users	Decompensation, death	Prevented decompensation HR 0.58 (0.34–0.98), decreased mortality HR 0.66 (0.33–0.86)	Low number of patients included, risk of selection and reporting bias. Biopsy proven cirrhosis
C. M-Feagans *Aliment Pharmacol Ther* 2013	US Veterans Health Admin	HCV and alcohol-related cirrhosis	Retrospective cohort study	2,468 statin users *vs.* 16,408 non-statin users	Simvastatin 90% Lovastatin 9%	3.3 years	Infections	Prevented infections aHR 0.67 (0.47–0.95)	Adjusted for age and comorbidities. No data of liver function

Randomised clinical trials

Study	Patient source	Patient description	Study design	Number of patients	Type of statin	Follow-up period	Endpoints	Results	Comments
Abraldes, *Gastroenterology,* 2009	University Hospitals	Cirrhosis and portal hypertension (HVPG >12 mmHg)	Multicentre randomised clinical trial (3 centres)	27 patients on statin treatment *vs.* 28 patients on placebo	Simvastatin	One month	Change in HVPG	Decreased HVPG from 18.5 to 17.1 (*p* = 0.003), not decrease in placebo group	Simvastatin administration improved quantitative tests of liver function (indiocyanine green clearance). Non-severe adverse events related to medication
P. Pollo-Flores, *Digestive and Liver Disease,* 2015	University Hospital	Cirrhosis and portal hypertension (HVPG >5 mmHg)	Single centre randomised clinical trial	14 patients under statins treatment *vs.* 20 patients on placebo	Simvastatin	Three months	Change in HVPG	Reduced HVPG in patients under statin treatment compared to placebo: −2 *vs.* 0 mmHg, *p* = 0.02	Previous variceal bleeding independent variable associated with response to simvastatin. Non-severe adverse events related to medication
Abraldes, *Gastroenterology,* 2016	University Hospitals	Cirrhosis and variceal bleeding 5–10 days before inclusion	Multicentre randomised clinical trial (14 centres)	69 patients under statin treatment *vs.* 78 patients on placebo	Simvastatin	Two years	Composite endpoint (rebleeding or death), death	Non-significant decrease in risk of rebleeding or death, decreased mortality HR 0.39 (0.15–0.98)	Decrease in liver-related death Non-significant decrease in the primary endpoint or in specific complications of cirrhosis
Bishnu, *Eur J Gastroenterol Hepatol,* 2018	University Hospital	Cirrhosis and portal hypertension	Single centre randomised clinical trial	11 patients atorvastatin + propranolol *vs.* 12 placebo + propranolol	Atorvastatin	One month	Change in HVPG	Decreased HVPG 4.81 ± 2.82 *vs.* 2.58 ± 1.88 mmHg	No significant differences in clinical outcomes after one-year follow-up

aHR, adjusted hazard ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; NA, not available; NASH, non-alcoholic steatohepatitis; OH, alcohol.

Clinical Trial Watch

statin membrane transporter named OATP1B1 that causes a reduction of the transport of statins and an increased exposure to these drugs.[83]

The safety of statins in patients with cirrhosis has been assessed in four RCTs that evaluated the effect of simvastatin or atorvastatin on portal pressure and incidence of gastrointestinal bleeding.[75–78] These studies included patients from all Child-Pugh classes (A, B and C), but the proportion of Child C patients was low and those patients with severe liver function impairment were excluded. No serious adverse events related to statins were reported in three of these studies,[75–77] however in the largest RCT of statins in patients with cirrhosis performed to date,[78] 2/69 patients treated with simvastatin 40 mg/day developed rhabdomyolysis. This potentially severe side effect should be taken into consideration in all new studies investigating the possible efficacy of statins in cirrhosis. Patients with advanced cirrhosis could theoretically be at increased risk because of the possibility of greater exposure to the drug due to impaired metabolism by CYP3A4 in the liver.[84,85] Additionally, reduced activity of the MRP2 membrane transporter, which is involved in statin transport to bile, has been described in patients with cirrhosis.[86,87] Finally, high bilirubin levels might interfere with the correct function of this protein and preclude an efficient statin clearance, which may result in an increased exposure to statins in patients with cirrhosis. However, this would require investigation in future studies. The safety profile of the treatment with statins in patients with cirrhosis is a relevant issue that will also be addressed in the Liverhope Clinical Trial, mentioned earlier [https://www.liverhope-h2020.eu/index_es.html].

Conclusion

There is increasing clinical interest in the use of statins for a number of chronic diseases beyond their traditional indications in cardiovascular disease. Statins have shown anti-inflammatory, antifibrotic and regenerative properties, which make them an exciting therapeutic option for chronic liver diseases. Initially, there were significant concerns relating to the safety of statins in patients with impaired liver function. However, cohort studies and small RCTs have provided growing evidence that statins are safe and potentially beneficial in patients with both pre-cirrhotic conditions and those with cirrhosis. Further RCTs are required, with larger patient series and hard clinical endpoints, before statins can be recommended for use in patients with chronic liver disease.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.07.019.

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Author names in bold designate shared co-first authorship

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