REVIEW

Statin therapy in patients with cirrhosis

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ABSTRACT

Cardiovascular disease is one of the leading causes of death among patients with cirrhosis and following liver transplantation. Although 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors ('statins') reduce the risk of cardiovascular events, fears about hepatotoxicity have historically led to underuse in patients with liver disease. In addition, the pharmacokinetics of statins can be significantly altered in cirrhosis, creating challenges with their use in liver disease. However, emerging data from randomised controlled trials and observational studies suggest that statin therapy appears to be safe and effective in patients with chronic liver disease and compensated cirrhosis. The cardiovascular risk benefits as well as the potential pleiotropic benefits of statins warrants strong consideration of use of statin therapy in patients with cirrhosis.

INTRODUCTION

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality among patients with all aetiologies of cirrhosis.[1 2] Several studies have reported CVD as the leading cause of non-liver-related mortality among patients with cirrhosis both in the transplant and non-transplant setting.[2–6] With the rising prevalence of cirrhosis from non-alcoholic fatty liver disease (NAFLD), the incidence of CVD among patients with cirrhosis is likely to rise as these patients are at an increased risk of CVD and frequently carry additional CVD risk factors including dyslipidaemia, diabetes mellitus and the metabolic syndrome.[7]

3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, or 'statins', represent a major breakthrough in the treatment and prevention of CVD and have been employed in clinical practice for more than 20 years. High-quality evidence from large randomised controlled trials supports the use of statins in primary and secondary prevention of CVD.[8–11] However, patients with liver disease were excluded from these trials limiting data on the role of statin therapy in this population. Concern about hepatotoxicity has historically led to decreased use of statins among patients with liver disease.[12]

Recent studies have demonstrated the efficacy and safety of statin therapy among patients with liver disease and cirrhosis.[13 14] Emerging evidence suggests multiple beneficial effects of statins in these patients independent of their lipid-lowering effects. Improvement in portal hypertension, reduction in the incidence of hepatocellular carcinoma (HCC) and delays in hepatic decompensation have been associated with statin therapy among patients with cirrhosis.[14–16] In this review, we will explore the burden of CVD among patients with cirrhosis, review available evidence on the safety and efficacy of statins in this population, and summarise recent studies demonstrating the pleiotropic effects of statins among patients with cirrhosis.

CARDIOVASCULAR RISK FACTORS AND MORTALITY IN CIRRHOSIS

Patients with cirrhosis frequently harbour traditional risk factors for CVD. Hypertension (53%), diabetes mellitus (51%), tobacco use (30%) and dyslipidaemia (22%) are frequent in patients with NAFLD cirrhosis.[17] CVD risk factors are also common among individuals with NAFLD listed for liver transplant (LT).[2 18 19] After LT, the frequency of these CVD risk factors increase with diabetes prevalence rising from 15%–21% pre-LT to 36%–37% post-LT, hypertension from 5.5%–17% pre-LT to 67%–72% post-LT and hyperlipidaemia found in 16.1% pre-LT and 59.9% post-LT.[2 18 19]

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Epidemiological studies have demonstrated significant cardiovascular morbidity among patients with cirrhosis. Sorensen *et al*[6] evaluated the causes of death among over 10 000 patients with cirrhosis from the Danish National Registry of Patients between 1982 and 1989. Causes of death were identified using the Danish Death Registry between 1982 and 1993. Overall, 69% of patients died with 51% of deaths attributed to complications of cirrhosis and 49% from other causes. CVD was identified as the leading cause of non-liver-related death comprising 8.8% of all deaths and 18% of non-liver-related deaths. When deaths secondary to other forms of heart disease, circulatory disease and cerebrovascular disease were included, 15.8% of overall deaths and 32.1% of non-liver-related deaths were attributed vascular disease.

These findings parallel those seen in LT recipients. Longitudinal studies evaluating patients undergoing LT identified CVD as a leading cause of death, accounting for 12.2%–21% of deaths after transplant.[2–5]

NAFLD is currently the third most common indication for LT in the USA and is projected to be the leading indication for liver transplantation by the year 2020.[19] Multiple studies have demonstrated higher prevalence of CVD risk factors, established CVD and higher rates of CVD events among patients with cirrhosis secondary to NAFLD compared with other causes of cirrhosis.[7 17] With the changing epidemiology of cirrhosis in the USA, there will likely be a parallel increase in CVD mortality among patients with cirrhosis with the rise of NAFLD. Identification and treatment of modifiable risk factors of CVD among patients with chronic liver disease and cirrhosis will be instrumental in the care of these patients.

USE OF STATINS IN CHRONIC LIVER DISEASE AND CIRRHOSIS

Statins reduce the incidence of CVD by altering lipid metabolism and through pleiotropic effects including improving endothelial dysfunction, decreasing inflammation and stabilising atherosclerotic plaques.[20]

In December 2013, the American Heart Association and the American College of Cardiology Foundation released revised guidelines on the treatment of cholesterol for CVD risk reduction.[21] Key features of these evidence-based guidelines include the abandonment of low-density lipoprotein cholesterol therapeutic targets, recommendation of statin therapy for all adults aged 40–75 years with diabetes, the use of risk calculation to determine eligibility for statin therapy and the use of different intensity of statin therapy based on individual CVD risk. Application of these new guidelines to National Health and Nutrition Examination Surveys data and extrapolation to the US population has demonstrated that roughly 12.8 million additional individuals should be considered for statin therapy.[22] Although these guidelines have not specifically been applied to cohorts of patients with recognised cirrhosis, it is likely that more individuals in this population should be considered for statin therapy as well.

Despite strong evidence supporting the use of statins in patients at increased risk for CVD, these agents have been underused among patients with chronic liver disease.[23 24] A retrospective review of patients with hepatitis C in the Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy trial reported that while 18% of patients had dyslipidaemia, only 2% of patients received statin therapy.[24] A recent survey of primary care physicians in the USA revealed that concern about statin hepatotoxicity in individuals with liver disease was a significant barrier to statin use.[12]

STATINS AND HEPATOTOXICITY

Mild asymptomatic elevations of serum aminotransferase levels may be seen in up to 10% of patients treated with statins, which appears to be a class effect.[23 25] The mechanism behind this effect is unclear, but may be related to depletion of hepatic mevalonate or one of its metabolites.[26] A moderate rise in serum aminotransferase levels, defined as an increase to >3× upper limit of normal (ULN), has been reported in 1%–3% of patients and does not differ from rates seen in the general population. Importantly, an increase in bilirubin, a superior marker of hepatotoxicity, is exceedingly rare and seen in <1% of patients.[27–30] In the Scandinavian Simvastatin Survival Study, among 2223 patients receiving simvastatin and 2221 receiving placebo with a median follow-up of 5.4 years, the rate of abnormal aspartate transaminase (defined as >3× ULN) was 0.9% in the statin group and 1.0% in the placebo group. The rate of abnormal alanine transaminase (ALT) was 2.2% in the simvastatin group and 1.5% in the placebo group (statistical significance not reported).[27] The Prospective Pravastatin Pooling Project reported similar rates of increased ALT (>3× ULN) among patients treated with pravastatin versus placebo (1.4% vs 1.4%, respectively, p=NS) with >112 000 person-years of exposure.[30] Similar findings have been reported among trials with other statins.[28 29]

The clinical significance of mild-to-moderate increases in serum aminotransferase levels seen with statin use is likely minimal. The National Lipid Association's Statin Safety Task Force Liver Expert Panel reported that based on available evidence statin-associated elevations in aminotransferase levels are not indicative of liver damage or liver dysfunction.[31] In addition, this group asserted that the presence of compensated cirrhosis was not a contraindication to statin therapy. In 2012, the US Food and Drug Administration (FDA) updated the recommendation for liver enzyme monitoring on statin labels, stating that routine monitoring of liver enzymes in patients taking statins is no longer

necessary. This recommendation was based on the observation that serious liver injury caused by statins is rare and unpredictable in individual patients.

SAFETY OF STATINS IN CHRONIC LIVER DISEASE

Initial trials assessing the CVD benefits of statin therapy excluded patients with underlying liver disease, leading to limited data in this population. A post hoc analysis of participants in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study sought to address this.[32] In this report, a subset of patients who entered the GREACE study with baseline abnormal aminotransferase levels (>1–3× ULN) who received statins were compared with placebo-treated patients. Participants with baseline abnormal aminotransferase levels who received statins had a 35% reduction in mean ALT ($p<0.0001$) compared with a 12% increase in ALT among those receiving placebo ($p=0.003$). In addition, statin treatment reduced the risk of CVD events by 68% among patients with baseline abnormal serum aminotransferase levels ($p<0.0001$). The abnormal baseline aminotransferase levels in these patients were attributed to NAFLD as patients with other causes of liver disease were excluded from this study. These results suggest that statin therapy is both safe and efficacious in preventing CVD among those with NAFLD.

Lewis *et al* performed a randomised controlled trial of high-dose pravastatin in patients with hyperlipidaemia and underlying liver disease (NAFLD 64%, hepatitis C 23% and <5% other causes) to assess lipid-lowering effects and hepatic safety. After 36 weeks, 7.5% of patients in the statin group had a doubling of ALT or increase in ALT>2× ULN compared with 12.5% of patients in the placebo group ($p=0.139$), suggesting no increased risk of liver injury with statin therapy in this population. Patients in the pravastatin group had a significant reduction in LDL (−25.85 vs −0.83 mg/dL, $p<0.0001$), cholesterol (−16.71 vs +1.28 mg/dL, $p<0.0001$) and triglyceride level (−6.32 vs +8.82 mg/dL, $p<0.0001$) compared with placebo. This study demonstrated the efficacy and safety of statin therapy among patients with underlying liver disease. Notably, patients with Child–Turcotte–Pugh (CTP) class B and C cirrhosis were excluded and the number of patients with CTP A cirrhosis was not reported in this study, thus limiting the generalisability to patients with cirrhosis.

While published data are limited, the use of statins among patients with compensated cirrhosis is relatively common. A study of the US Veterans Health Administration data from 2001 to 2009 determined that 13% of patients with compensated cirrhosis received new prescriptions for statins.[14] Kumar *et al*[33] evaluated the long-term safety of statin therapy among patients with compensated cirrhosis in a retrospective cohort study. Eighty-one individuals with biopsy-proven cirrhosis treated with ≥3 months of statins and 162 untreated individuals biopsy-proven cirrhosis with median follow-up duration of 36 and 30 months, respectively, were evaluated for hepatic decompensation (defined as development of ascites, bilirubin >2.5 mg/dL, encephalopathy, or variceal haemorrhage) and mortality. Statin therapy was significantly associated with lower risk of decompensation ($HR=0.58$, $p=0.04$) and mortality ($HR=0.53$, $p=0.01$). Though this was a relatively small observational study, these results support the use of statins among patients with compensated cirrhosis when clinically indicated for primary or secondary prevention of CVD.

STATINS AND PORTAL HYPERTENSION: MECHANISMS OF STATIN-MEDIATED REDUCTION IN PORTAL HYPERTENSION

Clinical and experimental preclinical studies have demonstrated that statins decrease portal hypertension through reducing intrahepatic vascular resistance. Increased intrahepatic vascular resistance is partly mediated by sinusoidal endothelial dysfunction driven by impaired endothelial nitric oxide synthase (eNOS) activity and increased sensitivity to endogenous vasoconstrictors.[34–37] Upregulated rho-kinase activity has been demonstrated in animal models of cirrhosis and in human liver tissue and may be responsible for this phenomenon.[36] Activation of this pathway inhibits myosin light chain phosphatase leading to a relative increase in phosphorylation of myosin light chains and increased vascular smooth muscle activity. Rho-kinase activation also suppresses eNOS expression and activity, further increasing vascular smooth muscle activity.[38]

Statins directly interfere with the formation of isoprenoid intermediates such as geranylgeranylpyrophosphate, which are required for membrane translocation of rhoA, a critical step in the rho-kinase pathway. Trebicka *et al*[34] used a bile duct ligation model of cirrhosis in rats to characterise the action of atorvastatin on hepatic vascular resistance. Molecular analysis revealed increased intrahepatic rho-kinase total protein levels in cirrhotic animals, but markedly decreased rho-kinase activity among animals treated with atorvastatin. Animals treated with atorvastatin also had increased eNOS expression compared with controls. Portal pressures were significantly decreased (>20% reduction, $p<0.05$) among animals treated with atorvastatin compared with controls with no difference in splanchnic or systemic vascular resistance. A study using a CCL4 model of cirrhosis in mice demonstrated reduced volume expansion-induced increases in portal pressure in animals treated with simvastatin compared with placebo.[35] Collectively, these results suggest that statins induce selective vasodilatation of the microvasculature in the cirrhotic liver. The ability of statins to selectively target hepatic microvasculature may offer a clinical advantage over other pharmacological therapies used to reduce portal

hypertension (β-blockers, nitrates) that can worsen systemic haemodynamics.

STATINS AND PORTAL HYPERTENSION: CLINICAL EVIDENCE OF STATIN-MEDIATED REDUCTION IN PORTAL HYPERTENSION

In a landmark proof-of-concept study, Abraldes *et al*[15] randomised 59 individuals with cirrhosis and severe portal hypertension (mean hepatic venous pressure gradient (HVPG) 19.8 mm HG placebo vs 18.5 mm HG treatment group) to 30 days of simvastatin or placebo. Simvastatin significantly decreased HVPG compared with placebo (−8.3% vs −1.6%, p=0.041). There were no differences in hepatic blood flow, mean arterial pressure or systemic vascular resistance between groups, suggesting that the change in portal pressure was mediated by a reduction in intrahepatic vascular resistance. Individuals treated with simvastatin also had improved markers of effective liver perfusion and hepatic metabolic capacity. There were no differences in adverse events between groups, and no patient had a more than a twofold increase in ALT at study completion. Three patients had an increase in creatine kinase (CK) of more than twofold (one patient in placebo group, two in simvastatin group). A multicentre randomised controlled trial to assess the efficacy of simvastatin in reducing portal hypertension and variceal bleeding has recently been completed and data analysis is underway.[39] While these emerging data on the role of statins and portal hypertension are promising, it would be premature to suggest that statins should be used at this time to reduce portal pressures.

STATINS AND HCC: POTENTIAL MECHANISMS OF STATIN-MEDIATED REDUCTION IN HCC

The mechanism of the observed chemoprotective effect of statins in reducing the incidence of HCC may be related to disruption of MYC signalling. Overexpression of MYC has been implicated in the pathogenesis of HCC in humans.[40] Statins interfere with the generation of isoprenoid intermediates, which decrease MYC phosphorylation and lead to impaired signalling through this pathway. Atorvastatin has been shown to suppress tumour growth in a transgenic mouse model of HCC through inhibition of MYC-mediated cellular proliferation.[41] Given the plausible physiological mechanism and suggestive clinical evidence, the use of statins as chemoprevention of HCC may be clinically useful among very high-risk patients.

STATINS AND HCC: CLINICAL EVIDENCE OF STATIN-MEDIATED REDUCTION IN HCC

Recent observational studies have demonstrated an association between statin use and reduced HCC risk.[42–44] Tsan *et al* reported a positive cumulative dose–response relationship between statin use and reduced HCC risk in a retrospective cohort study of 35 000 patients with hepatitis C virus using statins and 225 000 untreated patients. Adjusted HRs were 0.66 (p<0.001), 0.47 (p<0.001) and 0.33 (p<0.001) for patients with 28–89, 90–180 and >180 cumulative daily doses of statins per year compared with non-users. A subsequent meta-analysis reported that statin users were significantly less likely to develop HCC than non-users (OR 0.63, 95% CI 0.52 to 0.76).[16] When the relative risk reduction seen in this study is applied to a population at high risk for HCC (incidence of 3.7 per 100 person-years), the estimated number needed to treat to prevent one case of HCC per year is 73. Similarly, to statins and portal hypertension, it is currently premature to prescribe statins as chemopreventative agents in HCC.

PHARMACOKINETICS OF STATINS IN CIRRHOSIS

The pharmacokinetics of statins are complex and variable and detailed reviews on this topic can be found elsewhere.[45 46] It is important to note that while many statins are extensively metabolised by the cytochrome P450 system (lovastatin, simvastatin, atorvastatin), others use alternative pathways (pitavastatin) or undergo minimal metabolism prior to excretion (rosuvastatin and pravastatin). The often-extensive hepatic metabolism and predominantly biliary excretion of statins contribute to the altered pharmacokinetics of these drugs seen with progressive liver disease. Data on package inserts are available for five of the currently used statins regarding changes in maximum concentration (C_{max}) and area under the curve (AUC) among patients with CTP class A and B cirrhosis (table 1). Notably, marked elevations in atorvastatin (16-fold increase in C_{max} and 11-fold increase in AUC) are seen among patients with CTP class B cirrhosis. We could find no reports on the pharmacokinetics of simvastatin or lovastatin in patients with

Table 1 Changes in statin pharmacokinetics in cirrhosis*

Drug	Change in C_{max}	Change in AUC
Lipitor (atorvastatin)		
CTP class A	↑ 4.0-fold	↑ 4.0-fold
CTP class B	↑ 16.0-fold	↑ 11.0-fold
Crestor (rosuvastatin)		
CTP class A	↑ 1.6-fold	↑ 1.05-fold
CTP class B	↑ 2.0-fold	↑ 1.21-fold
Livalo (pitavastatin)		
CTP class A	↑ 1.3-fold	↑ 1.6-fold
CTP class B	↑ 2.7-fold	↑ 3.8-fold
Pravachol (pravastatin)		
Cirrhosis (CTP class not specified)	↑ 1.34-fold	↑ 1.52-fold
Lescol (fluvastatin)		
Cirrhosis (CTP class not specified)	↑ 2.5-fold	↑ 2.5-fold

*Currently available data from package inserts.
AUC, area under the curve; CTP, Child–Turcotte–Pugh.

cirrhosis through a search of the PubMed database or of the new drug applications of these drugs provided by the FDA. Caution should be used to prescribe the lowest clinically effective doses among patients with cirrhosis, particularly as a dose effect has been reported with the risk of statin-induced muscle injury and diabetes. The pharmacokinetics of statins in patients with CTP class C have not been reported, and use in this setting has been discouraged.[31] Medication interactions that involve statins may be enhanced in the setting of cirrhosis given altered statin pharmacokinetics. The Lexicomp online drug interaction database was used to identify an interaction between commonly used medications in patients with cirrhosis and all currently available statins.[47] Interactions with at least a risk rating of C or below are summarised in table 2. It is worth noting that these risk ratings are based on observations of drug interactions in patients without liver disease, and it is possible that the interaction may be altered in the setting of cirrhosis.

DIABETES RISK

Statin therapy has been associated with a small but statistically significant increased risk for the development of diabetes mellitus. A meta-analysis of 13 randomised controlled trials including more than 91 000 patients demonstrated a 9% increased risk for the development of diabetes mellitus with statin therapy.[48] The absolute increased risk was quite small at 0.39% after 4 years of statin exposure. When this risk is considered relative to CVD benefit, one additional case of diabetes occurs with 5.4 fewer major coronary events per 255 patients taking statins over 4 years. A subsequent meta-analysis of trials comparing high-to-moderate dose statin therapy including more than 32 000 patients demonstrated a 12% increased risk for the development of diabetes with high-dose statin therapy. The absolute increased risk was again small, and the authors reported a number needed to harm for intensive therapy of 498 and a number needed to treat to reduce CVD events of 155.

These studies demonstrate a small dose-dependent increased risk of diabetes with statin use that is far outweighed by observed CVD benefits seen in individuals at increased risk for CVD. When considering statin therapy to reduce CVD risk, it is clear that the cardioprotective effects outweigh an increased risk of diabetes. However, when considering statin therapy specifically for the treatment and prevention of complications of cirrhosis (portal hypertension and HCC), the relative risk of diabetes compared with clinical benefit may increase. Additional studies are needed to better characterise the protective effects of statins on complications of cirrhosis as well as the risk of incipient diabetes.[49]

MUSCLE INJURY RISK

Statins have been associated with a broad spectrum of muscle injury ranging from asymptomatic elevations in CK to rhabdomyolysis.[50] The overall risk of muscle injury is estimated to be between 5% and 10% for myalgias, >0.9% for myositis and >0.2% for rhabdomyolysis.[51–55] Well-established risk factors for statin-related muscle injury include a history of muscle pain during previous lipid-lowering treatment, unexplained muscle cramps, previous CK elevation, family history of muscle symptoms and hypothyroidism.[54] Mounting evidence suggests higher-dose statin

Table 2 Statin drug–drug interactions

Drug	Statins affected (risk rating)	Interaction	Mechanism
Cyclosporine	Atorvastatin (X), fluvastatin (D), lovastatin (X), pitavastatin (X), pravastatin (D), rosuvastatin (D), simvastatin (X)	Increased C_{max} and AUC of statins (all)	Inhibition of OATP1B1 transport (all), CYP3A inhibition (atorvastatin, lovastatin, simvastatin)
Boceprevir	Atorvastatin (D), fluvastatin (C), lovastatin (X), pitavastatin (C), pravastatin (C), rosuvastatin (C), simvastatin (X)	Increased C_{max} and AUC of statin (all)	Inhibition of OATP1B1 mediated transport (all), CYP3A inhibition (atorvastatin, lovastatin, simvastatin)
Telaprevir	Atorvastatin (X), fluvastatin (C), lovastatin (X), pitavastatin (C), pravastatin (C), rosuvastatin (C), simvastatin (X)	Increased C_{max} and AUC of statin (all)	Inhibition of OATP1B1 mediated transport (all), CYP3A inhibition (atorvastatin, lovastatin, simvastatin)
Norfloxacin	Atorvastatin (C), lovastatin (C), simvastatin (C)	Possible increased C_{max} and AUC of statin	Inhibition of CYP3A
Rifaximin	Atorvastatin (C)	Possible increase in C_{max} and AUC of rifaximin	Atorvastatin inhibits p glycoprotein
Spironolactone	Atorvastatin (C)	Theoretical reduction of endogenous steroid activity	Additive effects on reducing endogenous steroid activity
Tenofovir	Atorvastatin (C), lovastatin (C), simvastatin (C)	Possible decrease in C_{max} and AUC of statin	Induction of p glycoprotein

Information in this table gathered from the Lexicomp online drug interaction database. Lexicomp risk rating: (A) no known interaction, (B) no action needed, (C) monitor therapy, (D) consider therapy modification, (X) avoid combination.
AUC, area under the curve.

therapy confers a higher risk of muscle injury.[56–58] The most convincing evidence for this dose response comes from a randomised controlled trial comparing high-dose (80 mg) and low-dose (20 mg) simvastatin, which demonstrated increased risk of rhabdomyolysis among high-dose recipients (RR 26.6, p<0.0001).[56] Drug–drug interactions that raise serum statin levels have also been found to confer significantly increased risk of statin-related muscle injury.[59]

CONCLUSION

Patients with cirrhosis, particularly those with NAFLD, suffer from a high burden of CVD. However, current evidence suggests that statins are underused in patients with chronic liver disease despite several studies supporting the safety of statin use in patients with compensated cirrhosis. Furthermore, mounting evidence suggests that pleiotropic effects of statins in individuals with cirrhosis may improve portal hypertension and decrease HCC risk. Thus, it is imperative that clinicians understand the potential benefits, side effect profile and challenges of using statin therapy in patients with cirrhosis in order to maximise clinical efficacy and safety.

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