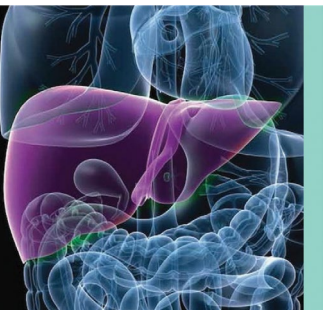

Statins Show Promise Against Progression of Liver Disease

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The cardiovascular and mortality benefit of statins, a class of cholesterol-lowering medications, represents one of the major medical breakthroughs of the 20th century. Further research into their robust benefits led to the discovery of novel molecular mechanisms and also beneficial clinical effects beyond cardiovascular disease. We previously reviewed the safety of statin use in chronic liver disease,[1] and here we review the growing scientific and clinical evidence suggesting benefit for statin use against the progression of liver disease.

STATIN MECHANISM OF ACTION: CLASSICAL VERSUS PLEIOTROPIC MODELS

In the 1960s, the search for cholesterol-lowering agents led Akira Endo to the initial discovery of statins. Nobel Prize–winning work by Michael Brown and Joseph Goldstein demonstrated the relationship between statin inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase and low-density lipoprotein (LDL) reduction. In the classical model, the clinical benefit of statins, such as myocardial infarction prevention, is attributed to lowered LDL.

As statin use expanded, novel biochemical and clinical benefits were discovered, leading to the development of the pleiotropic model that proposes multiple mechanisms for positive effect, both cholesterol dependent and independent.[2] Branching off cholesterol studies, downstream inhibition of isoprenoid intermediate formation was found to affect canonical Ras and Rho cascades, which later demonstrated benefit in cardiac fibrosis.[3] Both cardiac and vascular benefits are seen from statin vasodilatory effects via upregulation of endothelial nitric oxide synthase (eNOS).[4] Statins potentiate anti-inflammatory effects by mechanisms such as inhibition of macrophage protein kinase C signaling[5] and the phosphoinositide 3-kinase (PI3K)-AKT pathway, which also helps prevent malignancy (Fig. 1). Additional antitumor mechanisms include

Abbreviations: ALD, alcohol-related liver disease; ATV, atorvastatin; CI, confidence interval; eNOS, endothelial nitric oxide synthase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; HVPG, hepatic venous pressure gradient; IL, interleukin; KLF2, Kruppel-like Factor 2; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; PBC, primary biliary cholangitis; PI3K, phosphoinositide 3-kinase; PSC, primary sclerosing cholangitis; RCT, randomized clinical trial; SMV, simvastatin; TNF-α, tumor necrosis factor α.

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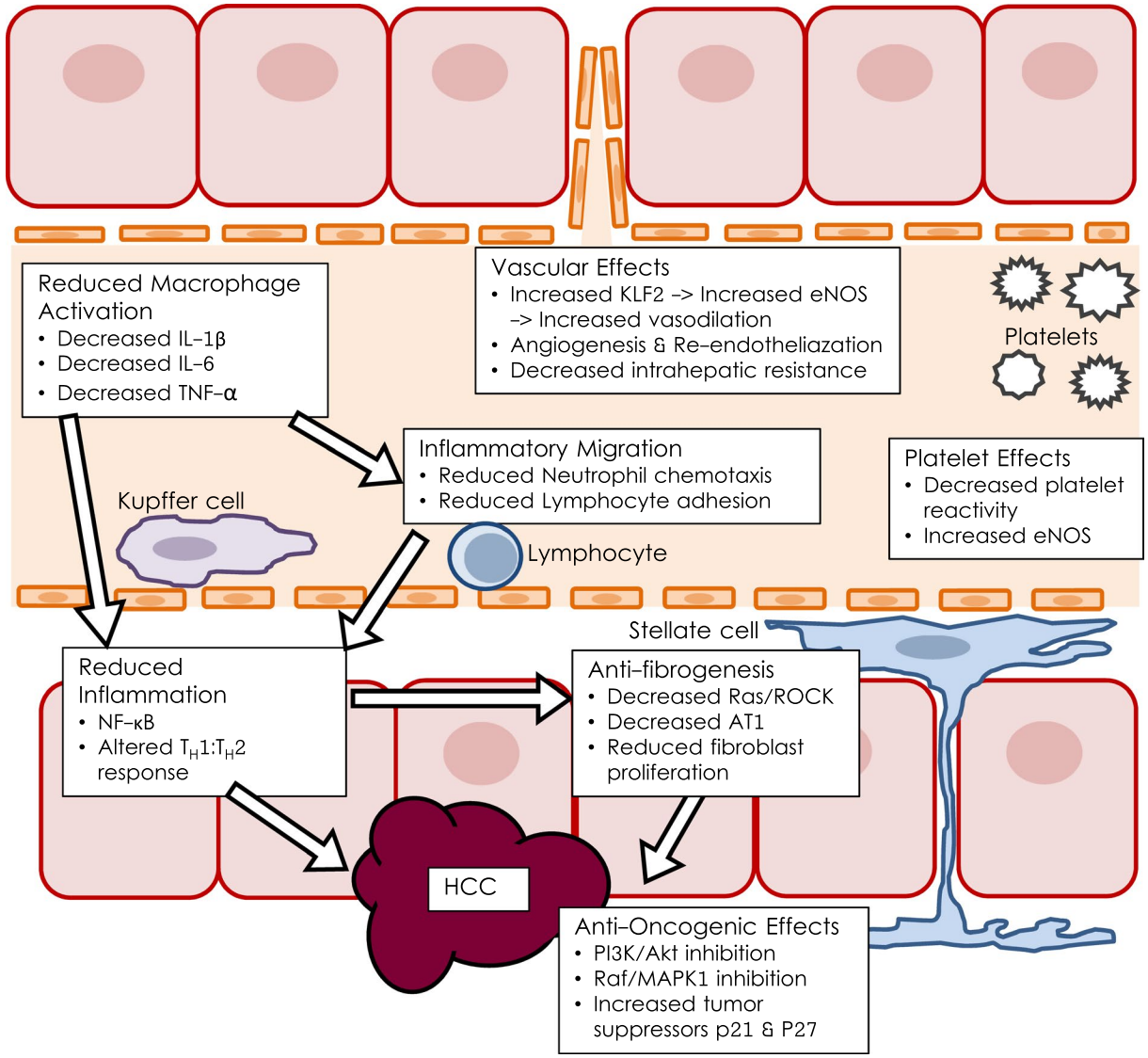

FIG 1 The pleiotropic model of statin mechanisms of action.

downregulation of the Raf/mitogen-activated protein kinase (MAPK) pathway, increasing persistence of tumor suppressors p21 and p27.[6]

These varied mechanisms bring biologic plausibility to observed benefits beyond cardiovascular disease. Through aforementioned broad Rho kinase signaling changes and more specific liver sinusoidal endothelial cell induction of Kruppel-like Factor 2 (KLF2),[7,8] statins were shown to increase endothelial nitric oxide production and decrease intrahepatic resistance, and thus portal hypertension, in cirrhotic rats.[9] In retrospective clinical data, decreased incidence of pancreatitis,[10] kidney disease,[11] and pneumonia[12,13] were observed. Small prospective trials showed benefit against venous thromboembolism[14] and brain atrophy in multiple sclerosis.[15] Emerging preclinical and clinical data show promise for use of statins in prevention and treatment of solid tumors, including prostate,[16] breast,[17] and colorectal cancers.[18-21]

VARIABLE BENEFITS OF STATINS IN DYSLIPIDEMIA AND CHRONIC LIVER DISEASES

Recent studies propose that statins may have an early benefit in certain chronic liver diseases. The most robust data are in nonalcoholic steatohepatitis (NASH), where statins are often already indicated for dyslipidemia or

cardiovascular risk.[22] In three randomized clinical trials (RCTs) evaluating cardiovascular outcomes with atorvastatin (ATV), *post hoc* analyses revealed improvement in liver enzymes and steatosis on imaging.[23] In both a retrospective, cross-sectional trial with a nested case control[24] and a small, pilot prospective study[25] of 20 patients with NASH, rosuvastatin showed improved NASH histopathology scores.

However, dyslipidemia alone does not dictate treatment. Primary biliary cholangitis (PBC) can cause hypercholesterolemia as a result of lipoprotein X, which is an antiatherogenic complex.[26,27] Large retrospective studies[28,29] and a 400-person prospective cohort study[30] show no increase in cardiovascular risk in PBC. Thus, although statin treatment is safe in PBC,[31] it is currently recommended only when warranted by cardiovascular risk.[32]

With benefits varying by disease etiology, recommendations for statin use early in chronic liver disease may similarly vary. Further, prospective studies and trials are needed to elucidate possible benefits and to define the clinical role of statins.

EVIDENCE FOR IMPROVEMENT IN PORTAL HYPERTENSION

Portal hypertension sequelae show clinical improvement when hepatic venous pressure gradient (HVPG) declines 20% or to less than 12 mm Hg. Statins improved intrahepatic resistance in mechanistic animal studies[9] and portal hypertension in five RCTs. Simvastatin (SMV) acutely decreased sinusoidal pressure in humans at 30 minutes via increased hepatic nitric oxide[33] through the aforementioned KLF2 pathway.[7,8] Similarly, at 1 month, SMV showed an 8.3% improvement in HVPG.[34]

A 2018 RCT of ATV in the setting of propranolol demonstrated HVPG reduction beyond nonselective beta-blocker effects. Although 90% of patients in the intervention arm (ATV and propranolol) reached target HVPG, the trial did not show a statistical or clinically relevant improvement in rebleeding, likely because of sample size limitations (n = 23).

STATINS ARE CORRELATED WITH SLOWED PROGRESSION OF LIVER DISEASE AND IMPROVED CLINICAL OUTCOMES

In six retrospective studies of patients without cirrhosis but with chronic liver diseases, including hepatitis B virus (HBV), hepatitis C virus (HCV), ethanol, and nonalcoholic fatty liver disease (NAFLD), statins such as lovastatin or ATV were associated with decreased progression to cirrhosis and decompensation, often in a dose-dependent manner (Table 1).[35-40] In patients with compensated cirrhosis, statins were associated with decreased progression to decompensated cirrhosis and death.[41,42] These benefits were strongly correlated to treatment length, with an 8% to 9% decrease in mortality for each year of treatment in Child-Pugh class A/B cirrhosis.[43]

A retrospective, population-based cohort study of patients with primary sclerosing cholangitis (PSC) with concomitant inflammatory bowel disease showed statin use to be associated with a reduction in all-cause mortality, as well as death or liver transplantation.[44] With no approved therapies for PSC, this promising finding has led to a clinical trial (ClinicalTrials.gov: NCT04133792).

Unfortunately, only one prospective RCT with a clinically relevant primary outcome has been completed. This 2016 prospective RCT compared SMV against placebo in patients with variceal bleed. No decrement in rebleeding (23.1% versus 20.3%) was observed; however, a benefit in transplant-free survival at 2 years (79.2% versus 89.4%) was observed.[45] Currently, there are multiple clinical trials recruiting in Europe, North America, and South America to further address the question of clinical benefit.

RETROSPECTIVE DATA SHOW STATINS MAY REDUCE INCIDENCE OF HEPATOCELLULAR CARCINOMA

In 2015, liver cancer was the sixth most diagnosed cancer worldwide with 854,000 new diagnoses and the fourth leading cause of cancer death with 810,000 deaths. Statins have shown evidence of decreasing incidence and recurrence of a variety of types of cancer. Mechanistic experiments suggest chemoprevention occurs via both classical inhibition of cholesterol synthesis[46] and also broader changes in canonical malignant signaling pathways and in multiple oncogene products with effects on inflammation, cellular migration,[47] invasion,[48] and angiogenesis[49] (Fig. 1).

More than 20 retrospective analyses have shown an association of statins with lower incidence of hepatocellular carcinoma (HCC) across various etiologies of liver disease (Table 2). This has been most intensely studied in

TABLE 1. PROSPECTIVE AND LARGE RETROSPECTIVE STUDIES ON STATINS IN LIVER DISEASE

	Year	Authors	Size (N)	Follow-up (months)	Statin Type	Etiology	Severity of Liver Disease	Change in Progression of Disease
Prospective	2009	Abraldes et al.[34]	59	1	SMV	ALD/HBV/HCV	Decompensated cirrhosis	Improved
	2015	Pollo-Flores et al.[64]	34	3	SMV	ALD/HBV/HCV	Decompensated cirrhosis	Improved
	2016	Abraldes et al.[45]	158	12	SMV	ALD/HBV/HCV/NASH	Decompensated cirrhosis	Improved
	2018	Bishnu et al.[65]	23	12	ATV	ALD/HBV/HCV/NASH	Decompensated cirrhosis	Improved
Retrospective	2008	Avins et al.[35]	93,106	29	Lovastatin	ALD/HBV/HCV/NASH	No cirrhosis	Improved
	2013	Motzkus-Feagans et al.[66]	19,379	40	Mixed* (90% SMV)	ALD/HCV	Compensated cirrhosis	Not measured
	2014	Kumar et al.[41]	243	36	Mixed (49% SMV)	ALD/HBV/HCV/NASH	Mixed cirrhosis	Improved
	2015	Hsiang et al.[67]	77,021	20	Mixed (85% ATV/SMV)	HBV	Compensated cirrhosis	Not measured
	2015	Butt et al.[36]	33,899	32	Mixed	HCV	No cirrhosis	Improved
	2015	Yang et al.[37]	226,856	90	Mixed	HCV	No cirrhosis	Improved
	2015	Dongiovanni et al.[24]	1201	N/A	Mixed	NASH	No cirrhosis	Not measured
	2016	Mohanty et al.[42]	40,512	30	Mixed (85% SMV)	HCV	Compensated cirrhosis	Improved
	2016	Oliver et al.[38]	5985	74	Mixed	HCV + HIV coinfection	No cirrhosis	Improved
	2016	Simon et al.[39]	47,459	98	Mixed	HCV	No cirrhosis	Improved
	2016	Huang et al.[40]	28,761	56	Mixed	HBV	No cirrhosis	Improved
	2017	Bang et al.[68]	24,748	67	Mixed	ALD	Mixed cirrhosis	Not measured
	2017	Chang et al.[69]	15,931	66	Mixed	ALD/HBV/HCV	Compensated cirrhosis	Not measured
	2019	Stokkeland et al.[44]	2914	66	Mixed	PSC	No cirrhosis	Improved

N/A, not applicable.
* Mixed refers to no cirrhosis, compensated cirrhosis, and decompensated cirrhosis.

TABLE 2. PROSPECTIVE AND RETROSPECTIVE STUDIES ON STATINS AND HCC

	Year	Author	Size (N)	Follow-up (months)	Statin Type	Severity of Disease	Results (HR, 95% CI)
Prospective	2019	Jouve et al.[56]	323	35	Pravastatin	Cirrhosis	No benefit versus sorafenib
	2020	Tran et al.[70]	475,768	55	Mixed*	Mixed	HCC reduction (0.61, 0.43-0.87)
Retrospective	2005	Friis et al.[71]	348,262	40	Mixed	No cirrhosis	Reduced cancer, HCC (0.86, 0.78-0.95)
	2008	Friedman et al.[72]	361,859	113	Mixed (75% lovastatin)	No cirrhosis	HCC reduction favored to be confounding
	2009	El-Serag et al.[50]	6518	29	Mixed	Mixed	HCC reduction (0.74, 0.64-0.87)
	2011	Chiu et al.[73]	2332	48	Mixed (46% ATV)	Mixed	HCC reduction (0.62, 0.42-0.91)
	2011	Marelli et al.[74]	91,714	55	Mixed	No cirrhosis	No change in total cancer risk
	2012	Tsan et al.[75]	33,411	12	Mixed	Mixed	Dose-dependent HCC reduction (0.53, 0.49-0.58)
	2013	Tsan et al.[76]	260,864	12	Mixed (47% ATV)	Mixed	Dose-dependent HCC reduction (0.47, 0.36-0.61)
	2014	McGlynn et al.[77]	562	132	Mixed	Mixed	HCC reduction (0.32, 0.15-0.67)
	2014	Björkhem-Bergman et al.[78]	105,715	54	Mixed (86% SMV)	No cirrhosis	HCC reduction (0.88, 0.81-0.96)
	2015	Chen et al.[79]	71,847	108	Mixed	Mixed	HCC reduction (0.28, 0.23-0.35)
	2015	Hsiang et al.[67]	73,499	24	Mixed (85% SMV, ATV)	No cirrhosis	HCC reduction (0.68, 0.48–0.97)
	2016	Simon et al.[39]	9135	168	ATV, fluvastatin	Mixed	Dose-dependent HCC reduction (0.60, 0.07-0.90)
	2017	Kawaguchi et al.[53]	734	132	Mixed	Mixed	Reduced HCC recurrence (0.34, $P = 0.005$)
	2017	Kim et al.[51]	1374	144	Mixed	Mixed	HCC reduction (0.36, 0.22-0.60)
	2018	Kim et al.[80]	9852	144	Mixed (67% SMV, ATV)	Mixed	HCC reduction (0.44, 0.33-0.58)
	2019	Menon and Mathew[81]	12,861	288	Mixed	Mixed	HCC reduction (0.993, 0.992-0.994)
	2019	Cho et al.[54]	347	60	Mixed	No cirrhosis	Reduced HCC recurrence (0.32, 0.11-0.89)
	2019	Simon et al.[57]	63,279	120	Lipophilic	Mixed	HCC reduction (0.56, 0.41-0.79)
	2020	Goh et al.[82]	7713	60	Mixed	Mixed	HCC reduction (0.36, 0.19-0.68)
	2020	German et al.[52]	102	168	Mixed	Cirrhosis	HCC reduction (0.20, 0.07-0.60)

*Mixed refers to no cirrhosis and cirrhosis.

viral hepatitis populations from Asia, but also from North America and Europe. Smaller studies in diabetes or NAFLD also show lower incidence of HCC for patients taking statins.[50-52] Intriguingly, in patients with HCC who underwent resection or transplantation, HCC recurrence was seen less frequently in patients taking statins.[53,54]

Unfortunately, there have been no prospective trials on statin chemoprevention of HCC. Retrospective analysis of cancer incidence in the prospective Prevention of Coronary Sclerosis trial, originally designed to evaluate cardiovascular events in 263 patients (179 on statins), was limited by low cancer incidence (17) with only 1 HCC case.[55] In the PRODIGE-11 trial for patients with HCC, pravastatin offered no clinical benefit.[56]

Notably, this lack of benefit from pravastatin could be explained by its hydrophilicity. Although no specific statin has shown a consistent benefit over other statins in all-cause mortality or progression of cirrhosis, multiple recent retrospective analyses have found that the benefit of HCC reduction was restricted to lipophilic statins.[57-59] These novel findings are supported by prior *in vitro* work showing the lipophilic statins fluvastatin[60] and SMV[61] inhibit cell-cycle progression and tilt the balance away from antiapoptotic Bcl-2 toward proapoptotic Bax.

POTENTIAL RISKS AND RECOMMENDED MONITORING

Prospective trials are needed not only to evaluate efficacy of statins in chronic liver disease but also to investigate pharmacokinetics and adverse effects in these unique populations. Recent meta-analyses have revealed a small but statistically significant increase in diabetes, with a number needed to harm of 225 patients (over 4 years) in one study[62] and an incidence rate of 2.2% (2 years) in another.[63] If statins induce diabetes in patients with diseases such as NASH, anticipated benefits could be negated.

Caution must be exercised when considering statins in decompensated cirrhosis, especially Child-Pugh class C. As hepatic function worsens, risk for myopathy and rhabdomyolysis increase. Although myalgias are common (5%-10%), true myositis (>0.9%) and rhabdomyolysis (>0.2%) are rare in patients without liver disease, mostly secondary to dosing and drug interactions. In advanced cirrhosis, the incidence of rhabdomyolysis was higher than predicted in patients receiving SMV (40 mg daily).[45] If statins are prescribed to these patients, close monitoring with routine serum creatine kinase screening is warranted.

CONCLUSION

Here we have reviewed the encouraging preclinical, retrospective, and prospective clinical data on statins as a chemopreventive therapy to slow liver disease progression and HCC. Although promising, we currently lack the large, prospective data needed to change guidelines regarding statin use in chronic liver disease. Fortunately, multiple clinical trials are currently recruiting that could provide the needed evidence.

Critically, if statins are otherwise indicated for cardiovascular risk, they are safe for use in chronic liver disease. We must continue to disseminate the importance of statins for patients with NASH and high cardiovascular risk despite largely unwarranted hepatic concerns. As data continue to emerge, statins may prove beneficial for many etiologies and stages of liver disease.

CORRESPONDENCE

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