MINI-REVIEW | Inflammation, Immunity, Fibrosis, and Infection

Rationale for the use of statins in liver disease

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STATINS ARE A CLASS OF competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for endogenous cholesterol and isoprenoid synthesis in the mevalonate pathway. Its inhibition leads to decreased production of precursors and subsequently reduction of cholesterol biosynthesis (Fig. 1A).

The so-called pleiotropic effects are mediated by the reduction of isoprenoids, such as farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate, necessary for the activation of small GTPases like Rho and Ras proteins (Fig. 1A). Statins diversely inhibit RhoA and Rac1 prenylation, modulating endothelial nitric oxide (NO) synthase (eNOS) and NO availability and enhancing stability of eNOS mRNA (Fig. 1B). This statin-dependent eNOS restoration can be also mediated by increased Krüppel-like factor-2 expression (28). Similar effects were observed in hepatic injury followed by fibrosis and cirrhosis. Moreover, statins decrease angiotensin II-induced oxidative stress in the liver (34) and enhance eNOS expression and activity by inhibiting RhoA membrane association (2, 52). Taken together, inhibition of GTPase prenylation and restoration of eNOS and NO availability are the key roles of statins in the improvement of vascular and endothelial function (Fig. 1B).

But also, the decreased cholesterol synthesis itself is beneficial severalfolds. Decreased cholesterol level leads to an increase of sterol regulatory element binding proteins, which act as transcription factors for the low-density lipoprotein (LDL) receptor that induces higher plasma LDL clearance because of an increased LDL receptor-mediated uptake and after lysosomal degradation of LDL (17). Also, the decreased hepatic triglyceride synthesis is possibly associated with activated peroxisome proliferator-activated receptor-α (PPARα) and increased β-oxidation activity (17) (Fig. 1C). Moreover, statins seems to beneficially modify PPARγ activity, which attenuates the production of tumor necrosis factor-α, interleukins-1β and -6, and C-reactive protein (CRP) (19, 46).

In summary, due to various mechanisms, dependent or not on the cholesterol levels, they modify pathological conditions as outlined in the following.

Statins in Cardiovascular Diseases

Statins also decrease LDL cholesterol levels, which are proatherogenic. For this reason statins have become standard of care in the treatment of diabetes and cardiovascular diseases (CVDs) to decrease or even reverse atherosclerosis. However, in liver diseases they are often underused even in high-risk
patients (9). Especially in CVDs, several studies have shown a clear effect of statins on inflammation. Besides the older Pravastatin Inflammation/CRP Evaluation (PRINCE) study, a recent study also demonstrated that statins improve inflammation and decrease interleukin-6 levels, a main regulator of CRP (19). Besides cytokine expression, statins exert anti-inflammatory properties in endothelial cells through modulation of activity and expression of metalloproteinases and adhesion molecules. Furthermore, statins directly inhibit the expression of major histocompatibility complex class-II molecules by interferon-γ (IFN-γ) in CD4+ helper T cells (TH1 cells), leading to a shift toward anti-inflammatory TH2 cell actions and beneficially modifying atherosclerosis. Moreover, as outlined above, statins improve eNOS and NO in endothelium, which decreases leukocytes chemotaxis, adhesion, and inflammation, key mechanisms aggravating atherosclerosis. The decreased infiltration of plaques by macrophages and down-regulation of proteolytic enzymes are also associated with decreasing NADPH oxidase isoform 2 (40).

While statins might inhibit the immune cell activity, they increase the number of circulating endothelial progenitor cells, which are important in the neovascularization of ischemic tissue, thereby contributing to the restoration of endothelial function (36). Furthermore, statins elicit antithrombotic effects downregulating platelet CD40L by inhibiting tissue factor activity and thrombin generation (17, 25). The modulation of inflammation, matrix remodeling, thrombosis, and vascular function improves prognosis of CVD patients treated with statins.

**Adverse Effects and Hepatotoxicity**

Although similar mechanisms as in CVD are involved in development and progression of liver disease, caution is required because of hepatotoxicity. Hepatic cells make a considerable contribution to cholesterol production and therefore are a major target of statins. The pharmacological activity and the hepatic metabolism of statins depend on their molecular structure and physical properties, such as lipophilicity, solubility, and absorption. Simvastatin, lovastatin, fluvastatin, and atorvastatin are metabolized by cytochrome P-450, while pravastatin, rosuvastatin, and pitavastatin remain almost unaffected by any hepatic metabolic processes.

The effect of statins on aminotransferase levels in the treatment of cardiovascular diseases was investigated in several studies with contradictory results. This inconsistency may be explained by pharmacogenetics and differences in the statins used. Although statins are generally well tolerated, reports about statin-induced liver injury can be found mainly for atorvastatin and simvastatin. However, this might be coincidental since these two statins are also the two most commonly prescribed ones (8).

The question whether statins have a hepatotoxic effect is considerably more relevant in patients with acute or chronic liver dysfunction. In a retrospective cohort study, lovastatin showed no increased risk of adverse hepatic effects in a total of 93,106 patients with liver disease. Another prospective, randomized, double-blind, placebo-controlled, multicenter trial investigated the safety of high-dose pravastatin in chronic liver disease. After 36 wk of treatment, alanine aminotransferase levels were even lower in the pravastatin-treated group (26). Furthermore, HMG-CoA reductase inhibitors were also found to be safe in patients after liver transplantation (29).

Few studies revealed that statin hepatotoxicity is a rare condition and might mimic an autoimmune phenotype of liver injury (4, 44, 45). However, in patients with chronic kidney diseases, the incidence of severe adverse events seems to be higher (38). Additionally, in most cases, the benefits of statins outweigh any potential hepatotoxic risks (8). Thus, comparing the benefits and risks of statin treatment individually could help to improve its efficacy.
CVDs in many patients are associated with metabolic syndrome, which in turn represents the ground of the development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Statins have been considered for treatment in NASH, and in recent years they have been generally evaluated as safe, even at high doses, leading to a wider use in patients (11, 26, 39). Nevertheless, studies assessing the beneficial effects of statins are scarce, mostly investigating only a small number of patients with different end points. These studies showed that statin therapy either attenuates inflammation and steatosis (15) or trends toward decreased fibrosis, whereas other studies found no change in fibrosis (15, 35). The different study outcomes may be due to the different statins used in the respective trials. Whereas atorvastatin at 10 mg/day for 24 mo elicited positive effects in NASH, simvastatin 20 mg/day over 12 mo had no effect in a similar cohort of patients (35). Moreover, genetic predispositions were disregarded by most of these studies and may provide additional explanation for the different outcomes regarding fibrosis. For example, a large multicenter study revealed that statin use in high-risk patients is beneficial, except in patients carrying the PNPLA3 I148M risk alleles (14). Thus genetic screening may be advisable for patients with NAFLD to ascertain the optimal therapy for each patient.

Recent studies revealed improvements of NASH and metabolic syndrome S after statin treatment (14, 16) (Table 1). Statins decrease LDL cholesterol levels in serum and, as a result, oxidized LDL levels that play an important role in NASH. As highlighted in Fig. 1C, statin therapy leads to decreased hepatic steatosis by decreasing LDL and activating sterol regulatory element binding proteins, PPARα, and β-oxidation (17). However, the anti-inflammatory effect of statins in NAFLD and NASH is partly attributed to activation of PPARγ and subsequent downregulation of proinflammatory mediators (19, 46). Additionally, the inhibition of small GTPase prenylation and diminished downstream signaling contribute to the anti-inflammatory features of statins (46). Recent experimental NASH studies further suggest a beneficial impact of statins in fibrosis. They inhibit the paracrine signaling of hepatocytes on hepatic stellate cells (HSCs), thereby inhibiting HSC activation and fibrogenesis during experimental NASH (12).

Additionally, with the hepatic and general metabolic improvement that are known to be tightly linked to chronic viral hepatitis C (HCV) infection, statins might exert direct antireplicative effect on HCV (21). Previous small-scale studies investigated the effect of statin monotherapy and revealed only mild antiviral effects (6). Especially in combination with direct-acting antiviral agents, statins may have an added value to the antiviral efficacy and mitigate the progression of HCV-related diseases, such as cirrhosis or hepatocellular carcinoma (HCC) (23, 37, 47, 57). Additionally, HCV patients with compensated cirrhosis under statin treatment seem to have a lower risk for decompensation as well as lower mortality (33) (Table 1).

Cholesterol synthesis and especially excretion might have an effect by default on biliary disorders. Increased cholesterol secretion contributed to gallstone formation, with possible complications such as cholangitis, cholecystitis or biliary pancreatitis, or chronic inflammatory processes in cholestasis. By contrast, secretion of cholesterol into the bile is reduced, which increase cholesterol serum levels and might further influence bile acid production and thereby lead to hepatic damage especially in primary biliary cholangitis (PBC) (10). Thus both disease complexes may be influenced by statins by decreasing biliary cholesterol secretion and serum cholesterol levels (Table 1). The antilithogenic effect of statins results from decreased biliary cholesterol secretion, reduced cholesterol saturation index, and thus reduced bile lithogenicity. Older studies suggest some additional benefits of statins in addition to ursodeoxycholic acid to prevent the development but not to treat established gallstones, and no novel insights have been lately established in the field. By contrast, statins reduce serum bile acid levels in bile duct ligated mice (13), at least partly because of activation of pregnane X receptor/sterol x receptor and PPARα. Moreover, statins sufficiently reduce serum LDL levels and cholesterol and may also improve vascular function in patients with PBC, without hepatic improvement, which might be also due to low numbers of patients (10, 50, 51). Therefore, further investigations should be performed to assess possible protective statin effects in patients with PBC.

Either NASH, HCV, PBC, or other etiology of liver disease have a common end stage, characterized by a profound liver remodeling and portal hypertension. Portal hypertension in cirrhosis arises by a mechanically increased intrahepatic resistance by narrowing of hepatic outflow (55). An additional dynamic component of increased intrahepatic resistance is

### Table 1. Statin effects in liver diseases

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<th>Liver Disease</th>
<th>Statin Effects</th>
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<tr>
<td>NAFLD/NASH</td>
<td>Decreased LDL serum levels, decreased hepatic inflammation, inhibited HSC activation, and decreased hepatic fibrosis</td>
<td>(11, 12, 14–17, 19, 26, 28, 35, 39, 46)</td>
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<tr>
<td>Chronic viral hepatitis C</td>
<td>Inhibited viral replication and increased LDL uptake</td>
<td>(6, 21, 23, 33, 37, 47, 57)</td>
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<tr>
<td>Hepatobiliary diseases</td>
<td>Decreased cholesterol secretion, decreased formation of cholesterol gallstones, and anomerolized cholestasis</td>
<td>(10, 13, 50, 51)</td>
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<tr>
<td>Liver fibrosis and portal hypertension</td>
<td>Inhibited HSC activation, decreased collagen production, decreased portal pressure, improved endothelial dysfunction, and induced senescence of HSC</td>
<td>(1–3, 5, 24, 27–29, 31, 41, 43, 52, 53, 58)</td>
</tr>
<tr>
<td>Noncirrhotic portal hypertension</td>
<td>Increased angiogenesis</td>
<td>(54, 56)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Inhibited proliferation, induced apoptosis, inhibited angiogenesis, and decreased HCC incidence</td>
<td>(6, 20, 22, 42, 47, 49)</td>
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Statins could not only improve different liver diseases but may also prevent the development of cirrhosis and its complications. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HSC, hepatic stellate cell; HCC, hepatocellular carcinoma.
dominated by an imbalance of vascular tone-regulating pathways, showing a shift toward vasoconstriction. Furthermore, RhoA and Rho-kinase signaling is responsible for the increased tone of the hepatic vasculature contributing to the activation of HSCs (58), the major contributor to ECM synthesis upon chronic liver injury (18, 30). Statins modulate the mechanic and the dynamic intrahepatic pathways. Both pathways represent targets of statin therapy in liver cirrhosis with portal hypertension (Fig. 1B). Atorvastatin inhibits the translocation of RhoA and thus the activity of Rho-kinase (29). This effect decreases collagen production and HSC activation in early fibrosis as well as proliferation, cytokine production, and contraction of activated HSCs in cirrhosis (52, 53). Importantly, statins might induce senescence in activated HSCs, leading to a decreased turnover of these highly active cells (24, 52, 53). Simultaneously, statins improve endothelial dysfunctions by upregulated activity of eNOS and NO availability in cirrhotic livers and further decrease portal pressure (2, 52). Statin-induced upregulation of eNOS is mediated by Krüppel-like factor 2 to decreased HSC activation and lower portal pressure (27, 28) (Table 1).

In several small-scale human studies, acute and chronic effects of simvastatin on portal pressure were investigated (1, 41). All studies show a significantly decreased hepatic vascular resistance in cirrhosis with portal hypertension, which was additional to the extrahepatic effect of β-blockers (1).

Another recent study confirmed the beneficial effects of statins, even in patients identified as nonresponder to nonselective β-blockers (5). Besides decreased portal pressure, cirrhotic patients under statins may also benefit from improved liver function. Interestingly, statin effects are enhanced with increased severity of portal hypertension (41). In addition, simvastatin improved survival in patients after variceal hemorrhage while no effect was observed on the rebleeding rate, suggesting multiple beneficial effects of statins (3). As demonstrated in an animal model (31), the severity of hemorrhage might also be lower in patients receiving statins. Moreover, the toxicity of statins was less observed as liver damage, but mainly as myopathy (3), which might be prevented and attenuated by novel statin drugs, as suggested by using a compound containing atorvastatin and an NO donor (43).

Portal hypertension might also result from obstruction of the liver venous inflow or outflow (54). In noncirrhotic portal hypertension, contrary to its effects in cirrhotic portal hypertension, statins might enhance splanchnic vascular hyperperfusion because of increased angiogenesis in noncirrhotic portal hypertension mediated by an upregulation of the Hedgehog pathway (56). Although cirrhotic and noncirrhotic portal hypertension share end points, the origin of portal hypertension and the grade of liver disease possibly have a crucial impact on the treatment success. Hence, this study suggests caution when using statins in noncirrhotic portal hypertension.

As mentioned before, especially in HCV cirrhosis, statins might exert antimalignant properties. Besides inhibition of proliferation in vitro, statins might also induce apoptosis of hepatoma cells and inhibit intrahepatic angiogenesis (Table 1). Reduced proliferation might be due to interferences with K-ras and prevention of p21 and 27 breakdown in malignant cells, followed by induction of cell-cycle arrest. Specific interference with integrins and Rho-kinase, which are expressed at the cell membrane, was shown to reduce proliferation as well as tumor cell adhesion in an in vitro HCC model (42). These effects are mainly attributed to reduced RhoA activation and subsequently Rho-kinase inhibition (Fig. 1). Recent studies report a highly significant decrease in HCC risk resulting from statin use (47, 49). The recently published data from the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) database show a dose-dependent reduction of fibrosis progression as well as HCC incidence. Remarkably, reduction of HCC incidence was ~47% in all treated patients. Also, this study clearly showed differences in statin efficacy, whereby atorvastatin and fluvastatin had the strongest effects on fibrosis progression, as well as HCC incidence (47). Nonetheless, it remains uncertain whether these effects are due to fibrosis reduction, direct effects on HCC progression, or a combination of both. It should also be taken into account that statins might have antiviral properties due to reduction of HCV replication, additionally contributing to benefits observed in the ERCHIVES patients (6). Therefore, future studies are required to further evaluate statin therapy in the prevention of HCC.

Besides prevention of HCC incidence, pravastatin attenuates the progression and metastatic behavior of HCC because of decreased metalloproteinase activity. Additionally, statins hamper Ras signaling and also decrease cholesterol production. The cholesterol content of mitochondrial membrane, which may be crucial in the development of chemoresistance in HCC, is also reduced by statins (Table 1). The data in this context are limited and controversial. While recently published findings analyzing patients with early stage HCC showed no significant difference in survival related to statin treatment (20), the additional effect of statins on chemotherapy as well as transarterial chemoembolization treatment could be beneficial in patients with HCC (22).

Summary/Conclusion

Statins exhibit pleiotropic effects in many liver diseases. One of these effects is the inhibition of isoprenoid synthesis as a consequence of decreased HMG-CoA reductase activity, since the resulting modulated GTPase activity plays a major role in the treatment of most chronic liver diseases (Table 1). Statins are cost effective, generally well tolerated by patients, and the benefits of statin treatment in most patients outweigh their potential hepatotoxic risk. Especially in patients with severe chronic liver injury and high risk of CVD, statin treatment is very promising since it not only prevents the development of CVD but also could help to prevent the progression of liver fibrosis to cirrhosis and HCC with all the concomitant complications. Therefore, the reasons for statin use in chronic liver diseases are more convincing than the reasons against, rendering statin treatment a definite advantage.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
REFERENCES


