



Statins for cirrhosis: almost ready for clinical application

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Past

Liver cirrhosis is often diagnosed at a late stage, where development of complications such as infections, ascites, hepatic encephalopathy, and variceal bleeding indicate a worsened prognosis (1). Once complications occur, the two-year survival is 50 % and presence of systemic inflammation further predisposes to an excess risk of infections and mortality (2).

Medical treatment of liver cirrhosis has traditionally focused on isolated complications such as ascites, variceal bleeding, and hepatic encephalopathy (3), and to a lesser extent on causal factors leading to progression of the disease. Only few randomized trials have evaluated pharmacological principles of treatment addressing causal factors such as combination therapy with effect on systemic inflammation and portal hypertension within the recent years (4,5).

More than two decades ago statins were shown to have a potent anti-inflammatory effect and more recently pathophysiological and clinical studies have demonstrated a potential clinical benefit by adding statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) to the standard treatment regimens for cirrhosis. Statins partly act by improving endothelial dysfunction by increasing the Nitric Oxide (NO) production (6). In cirrhosis, the endothelial NO release is impaired in the liver microvasculature and is a major contributor to the increased hepatic resistance and development of portal hypertension (7).

This recognition led to a series of experimental studies

demonstrating a decrease in intrahepatic vascular resistance and an improvement of the vasculature in the cirrhotic rat liver, mediated by an up-regulation of NO production in the liver vasculature (8,9). Apart from increasing the hepatic NO production statins may also inhibit fibrogenesis in cirrhotic rats (10). The lowering effects of statins on portal pressure were published in 2004 followed by a series of studies that assessed the beneficial effects of simvastatin on portal hypertension (11-13).

Lately, a large randomized trial showed a beneficial effect of simvastatin on survival, but not on the risk of rebleeding from esophageal varices in patients with cirrhosis (14).

Rifaximin, a nonabsorbable antibiotic exerting a broad-range of antimicrobial activity, has a significant beneficial effect on prevention of hepatic encephalopathy (15). Rifaximin may modulate the human gut microbiome preventing bacterial translocation and systemic inflammation, and hence exert a positive effect on portal hypertension (4,16,17).

A possible synergistic effect of rifaximin, and simvastatin may improve endothelial dysfunction as well as fibrogenesis, and would therefore represent a new treatment principle for the prevention of disease progression in liver cirrhosis.

Present

Recently Pose *et al.*, studied the potential benefits of combination therapy with rifaximin and simvastatin for prevention of decompensated cirrhosis (18). The main aim

of this randomized, double-blind and very-well conducted trial was safety.

Fifty patients with decompensated liver cirrhosis were randomized to simvastatin 20 mg + rifaximin 1,200 mg, simvastatin 40 mg + rifaximin 1,200 mg or placebo of both drugs.

In the simvastatin 40 mg + rifaximin 1,200 mg group three of 16 patients had a three-fold increase in ALT or AST, and one patient developed drug-induced liver injury. Three patients had a five-fold increase in creatine kinase. Only one patient had increasing AST or ALT in the simvastatin 20 mg + rifaximin 1,200 mg group, and none in the placebo group. These numbers led to the conclusion that simvastatin in dose of 20 mg has a good safety profile and that higher doses should be avoided in decompensated cirrhosis. However, the present study observed a higher number of adverse events compared to previous randomized trials (11,12,14). This might be explained by the more advanced stage of cirrhosis among the trial participants and a possible toxic effect of rifaximin (18). Rifaximin extended intestinal release 400 mg, was used. This formulation allows for a higher bioavailability in the intestine. Pose *et al.* did not include a rifaximin + placebo group in the trial. The primary focus area of the trial was the potential synergistic effect of simvastatin and rifaximin.

A recent registry study have demonstrated that statins reduce the risk of hepatic decompensation and mortality in alcohol-related and viral-induced cirrhosis (19). Retrospective studies have also shown a potential beneficial effect on risk of infections and hepatocellular carcinoma (19,20).

At present, evidence is accumulating to support the notion that statins in small doses are relatively safe and may prevent complications and even mortality in cirrhosis. Yet, some concerns need attention before statins may be included in future guidelines and clinical treatment.

Future

The present study by Pose *et al.* is conducted in patients with decompensated cirrhosis.

The study raises a main concern of safety and tolerability of statins in decompensated liver disease. Safety, as well as direct effects of statins on the pathophysiological mechanisms that drive decompensation needs further exploration in the future (21).

Atorvastatin is a potent 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, with less toxicity, and a better safety profile than simvastatin (22). Further, there

seems to be a beneficial inhibitory effect on development of cirrhosis and hepatocellular carcinoma as well as similar beneficial effects on portal hypertension as simvastatin (23). Future studies should assess efficacy of atorvastatin on clinical endpoints in cirrhosis such as portal hypertension, decompensation, biochemistry, mortality, hospitalization (24).

Traditionally, management of patients with cirrhosis has focused on symptom relief and treatment of complications in cirrhosis. From a pathophysiological point of view implementation of statins in the treatment regimen is highly relevant when focus is directed towards potential inhibition of fibrogenesis and amelioration of hepatic circulation and portal hypertension with prevention of hepatic decompensation and other complications as the outcome. To clarify these aspects there is a high demand for large clinical randomized trials of patients with compensated cirrhosis with registration of clinical endpoints such as hospitalizations, time to decompensation, and survival.

The mechanisms of action of statins, the pathophysiological impact and efficacy in the human hepatocyte is still largely unknown. Further exploratory trials addressing the direct cellular effects of protein activation and metabolic activity of statins in endothelial cells is of high interest. Hepatocyte activity assessed by novel technologies of metabolomics and proteomics, is highly warranted and may be useful in future application of precision medicine in cirrhosis.

Some answers may be provided from the future StatLiver trial (24). This randomized clinical trial comparing atorvastatin versus placebo will address both clinical endpoints such as survival, decompensation and portal hypertension, as well as exploratory outcomes of transcriptomics and protein activity in liver tissue.

In decompensated patients the anti-inflammatory mechanisms of statins are scarcely investigated both in relation to effect on local inflammation in the liver and to effect on systemic inflammation is. In a large sequel of the study by Pose *et al.*, the Liverhope-Efficacy study, anti-inflammatory mechanisms of simvastatin will be explored, and provide novel insight into prevention of Acute-on-chronic-liver-failure and cirrhosis complications (25).

In conclusion, the results of the study by Pose *et al.* have provided new insights into the safety of statins for cirrhosis and revealed inspirational knowledge for the design of future clinical trials assessing both clinical endpoints and pathophysiological efficacy of statins on systemic inflammation and cellular mechanisms in the liver. Future studies may support clinical application of statins in the treatment of liver cirrhosis.

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References

- Jepsen P, Ott P, Andersen PK, et al. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010;51:1675-82.
- Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;64:1249-64.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406-60.
- Kimer N, Pedersen JS, Busk TM, et al. Rifaximin has no effect on hemodynamics in decompensated cirrhosis: A randomized, double-blind, placebo-controlled trial. *Hepatology* 2017;65:592-603.
- Fernández J, Claria J, Amoros A, et al. Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic Inflammation in Patients With Decompensated Cirrhosis. *Gastroenterology* 2019;157:149-62.
- McGirt MJ, Lynch JR, Parra A, et al. Simvastatin increases endothelial nitric oxide synthase and ameliorates cerebral vasospasm resulting from subarachnoid hemorrhage. *Stroke* 2002;33:2950-6.
- Gupta TK, Toruner M, Chung MK, et al. Endothelial dysfunction and decreased production of nitric oxide in the intrahepatic microcirculation of cirrhotic rats. *Hepatology* 1998;28:926-31.
- Abraldes JG, Rodriguez-Vilarrupla A, Graupera M, et al. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. *J Hepatol* 2007;46:1040-6.
- Trebicka J, Hennenberg M, Laleman W, et al. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. *Hepatology* 2007;46:242-53.
- Chong LW, Hsu YC, Lee TF, et al. Fluvastatin attenuates hepatic steatosis-induced fibrogenesis in rats through inhibiting paracrine effect of hepatocyte on hepatic stellate cells. *BMC Gastroenterol* 2015;15:22.
- Abraldes JG, Albillos A, Banares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009;136:1651-8.
- Pollo-Flores P, Soldan M, Santos UC, et al. Three months of simvastatin therapy vs. placebo for severe portal hypertension in cirrhosis: A randomized controlled trial. *Dig Liver Dis* 2015;47:957-63.
- Zafra C, Abraldes JG, Turnes J, et al. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. *Gastroenterology* 2004;126:749-55.
- Abraldes JG, Villanueva C, Aracil C, et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. *Gastroenterology* 2016;150:1160-70.e3.
- Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*

- 2010;362:1071-81.
16. Bajaj JS. Review article: potential mechanisms of action of rifaximin in the management of hepatic encephalopathy and other complications of cirrhosis. *Aliment Pharmacol Ther* 2016;43 Suppl 1:11-26.
 17. Kalambokis GN, Mouzaki A, Rodi M, et al. Rifaximin improves systemic hemodynamics and renal function in patients with alcohol-related cirrhosis and ascites. *Clin Gastroenterol Hepatol* 2012;10:815-8.
 18. Pose E, Napoleone L, Amin A, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol* 2020;5:31-41.
 19. Chang FM, Wang YP, Lang HC, et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: A population-based study. *Hepatology* 2017;66:896-907.
 20. Motzkus-Feagans C, Pakyz AL, Ratliff SM, et al. Statin use and infections in Veterans with cirrhosis. *Aliment Pharmacol Ther* 2013;38:611-8.
 21. Pose E, Trebicka J, Mookerjee RP, et al. Statins: Old drugs as new therapy for liver diseases? *J Hepatol* 2019;70:194-202.
 22. Yebyo HG, Aschmann HE, Kaufmann M, et al. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. *Am Heart J* 2019;210:18-28.
 23. Simon TG, Bonilla H, Yan P, et al. Atorvastatin and fluvastatin are associated with dose-dependent reductions in cirrhosis and hepatocellular carcinoma, among patients with hepatitis C virus: Results from ERCHIVES. *Hepatology* 2016;64:47-57.
 24. Kimer N, Gronbaek H, Fred RG, et al. Atorvastatin for prevention of disease progression and hospitalisation in liver cirrhosis: protocol for a randomised, double-blind, placebo-controlled trial. *BMJ Open* 2020;10:e035284.
 25. Pitch J. Efficacy of the Combination of Simvastatin Plus Rifaximin in Patients With Decompensated Cirrhosis to Prevent ACLF Development (2018-001698-25). *Clinicaltrials.gov*. 2020. Available online: <https://clinicaltrials.gov/ct2/show/NCT03780673?cond=NCT03780673&draw=2&rank=1>

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