

Statins in cirrhosis – ready for prime time

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Manuscripts

Review

Statins in cirrhosis – ready for prime time

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3 Statins are inhibitors of the HMG-CoA reductase with lipid-lowering properties
4 that are routinely prescribed for primary and secondary prevention of
5 cardiovascular events (1). In recent years, experimental and observational
6 studies have demonstrated that statins have pleiotropic effects over and above
7 their anti-lipid mechanism of action, and have been proposed as part of potential
8 preventative strategies for decompensation in cirrhosis (1).
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17 There is a strong experimental rationale for such strategies. From a mechanistic
18 perspective, simvastatin increases nitric oxide (NO) availability in the cirrhotic
19 liver circulation by enhancing the expression and activity of endothelial NO-
20 synthase and therefore ameliorates portal hypertension, but also prevents
21 endothelial dysfunction during endotoxaemia (2). An anti-inflammatory effect is
22 achieved through a decreased production of inflammatory cytokines and
23 leukocyte migration to the sub-endothelial space. Importantly, mainly mediated
24 by upregulation of the nuclear receptor KLF2, statins have anti-fibrotic effects
25 due to inhibition of hepatic stellate cell activation by its paracrine interaction
26 with endothelial sinusoidal cells (3).
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40 In their article in *Hepatology*, Chang and co-authors used the Taiwan National
41 Health Insurance database in a nested case-control study to estimate the effect of
42 statins on the risk of decompensation, mortality and HCC in patients with
43 cirrhosis. Index cases of cirrhosis were identified from a representative sample
44 of 1,000,000 people who were followed from 2000 to 2013 (4). The authors used
45 propensity score matching and finally selected 675 patients with cirrhosis in
46 each of the statin-user and non-statin user group from a potential size of 1172
47 statin users. HCV, HBV and alcohol were the included aetiologies of cirrhosis.
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3 defined daily dose (cDDD) of any statin. Statin users and non-users were well
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5 matched in baseline characteristics including the Charlson comorbidity index.
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7 Use of statins was associated with a significantly lower risk of decompensation
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9 (HR 0.39), mortality (HR 0.46) and HCC development (HR 0.52) in a dose-
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11 response relationship in the overall cirrhotic population, with users with a
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13 cDDD>365 days having the greatest benefit. When analysed according to the
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15 aetiology of cirrhosis, statin use was associated with a reduced risk of
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17 decompensation in HBV and HCV and a trend for lower risk of decompensation
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19 in ALD, but no change in the risk of mortality or HCC in independent aetiologies
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21 (likely due to lower number of patients/events in this sub analysis).
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26 An advantage of this study compared to other population studies is that it
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28 derives from a well-validated general population database, thus significantly
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30 reducing the risk of selection bias. There are inevitable weaknesses as with such
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32 retrospective analyses, which include the lack of patients with NASH cirrhosis,
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34 the absence of laboratory parameters (with ensuing inability to calculate and
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36 correct for the MELD and Child-Pugh score), a potential lead-time bias for the
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38 incident HCC cases and the low threshold (cDDD>28) to classify a patient as
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40 statin user. Nevertheless, the propensity score matching was robust and non-
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42 bleeding varices at baseline was added in the model to account for the presence
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44 of clinically significant portal hypertension. The dilution of the statin effect in
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46 individual aetiologies of cirrhosis is most likely due to type II error rather than
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48 selective effectiveness in viral hepatitis over alcohol-induced cirrhosis.
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53 This study adds further observational evidence on the potential beneficial effects
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55 of statins in patients with cirrhosis. In large cohort studies, statin use was
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57 protective against significant fibrosis in patients with NAFLD (5) and was
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3 associated with approximately 50% lower risk of progression to cirrhosis in
4 patients with HCV (6) and HBV (7). In a cohort of 40,512 patients with
5 compensated HCV cirrhosis, statin use was associated with a 40% lower risk of
6 decompensation and death (8). Statins have also been associated with reduced
7 risk for the development of hepatocellular carcinoma in various liver disease
8 aetiologies (1). Importantly, these studies suggest that such effects are class
9 effects rather than related to a particular statin and apply to all non-cholestatic
10 aetiologies of cirrhosis. However, even promising, these studies need
11 confirmation by prospective randomized clinical trials (RCTs).

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23 There have been two proof of concept prospective RCTs on the use of statins for
24 cirrhosis so far. In a RCT of 59 patients, simvastatin given for one month
25 significantly reduced portal pressure by an average of 8.3% and was associated
26 with a marked improvement in liver indocyanine-green clearance, indicating a
27 potential for improved liver function (9). Importantly, the effect on portal
28 pressure was over and above that of non-selective beta-blockers. In a further
29 RCT in 158 patients with decompensated cirrhosis due to previous variceal
30 bleeding, addition of simvastatin to standard of care was independently
31 associated with a survival benefit (HR=0.55) in those patients with Child Pugh A
32 and B cirrhosis (10). The study is an important guidance to further study design;
33 although the primary composite endpoint of reduction of rebleeding or death
34 was not achieved, simvastatin had a significant effect in all cause mortality,
35 mostly due to less bleeding or infection-related deaths, further reinforcing the
36 pleiotropic statin effect (10). This is in keeping with data from pre-clinical
37 cirrhotic models showing that statins protect from liver failure secondary to
38 sepsis and hypovolemic shock (2). In the BLEPS study, statins were no beneficial
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3 in patients with Child-Pugh C cirrhosis (10). Moreover, there were 2 cases of
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5 statin-induced rhabdomyolysis in Child-Pugh C patients compared to no cases in
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7 Child Pugh A or B thus raising efficacy and safety concerns in patients with more
8
9 advanced liver disease. Figure 1 shows the potential beneficial effects of statins
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11 in the evolution of cirrhosis and combines the presented data.

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14 The above evidence justifies a phase III RCT of statins in patients with cirrhosis.
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16 Such a trial should only include compensated patients with Child-Pugh A (and
17
18 potentially Child Pugh B7) with the primary endpoint being a composite
19
20 outcome of decompensation or death. Given the fact that most statins are
21
22 inexpensive and generic drugs, public funding would be required. In an era of
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24 increasingly expensive medications with profound impact on healthcare budgets,
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26 exploring the repurposing of statins for cirrhosis is a too good opportunity to be
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28 missed.
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3 **Figure 1.** Potential impact of statins on the evolution of chronic liver disease.
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5 Transition from chronic liver disease to compensated cirrhosis is driven by
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7 fibrogenesis, while progression from compensated to decompensated cirrhosis is
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9 mainly driven by complications of portal hypertension. Both disease drivers may
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11 be attenuated or prevented by statins. Statins may also prevent further
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13 decompensation due to sepsis and to gastrointestinal bleeding, however there is
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15 an efficacy and safety concern in patients with Child Pugh C.
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19 HCC: hepatocellular carcinoma; SBP: spontaneous bacterial peritonitis
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