First isolated from *Penicillium citrinum* by Akira Endo\(^1\) and colleagues, statins were a breakthrough drug class of serum low-density lipoprotein (LDL)-lowering agents, subsequently demonstrating efficacy in prevention of cardiovascular disease and mortality.\(^2\) As other LDL-lowering therapies showed more modest benefits in patient-centered outcomes, data have emerged showing a range of pleiotropic effects that drive these benefits.\(^3\)

Early trials also revealed associated transaminase elevations.\(^4\) The concerns for hepatotoxicity initially led to US Food and Drug Administration (FDA)-mandated hepatic monitoring and reluctance to prescribe in the setting of pre-cirrhotic chronic liver disease and cirrhosis.\(^5\) These concerns stand opposed to the potential benefits for these patients, especially as cardiovascular morbidity and mortality are increasingly understood in this population. In this article, we review the evidence on the safety of statin use and find that statins are generally safe in the liver for patients ranging from healthy to those with compensated cirrhosis, with caution needed in patients with decompensated cirrhosis.

**TRUE HEPATOTOXICITY IS RARE IN PATIENTS WITHOUT UNDERLYING LIVER DISEASE**

In early clinical trials, rises in serum transaminases were noted in approximately 10% of patients, leading to concerns for clinical hepatotoxicity, which was observed at supratherapeutic doses in preclinical animal studies.\(^4,6\) Hepatic adverse events were initially defined as alanine aminotransferase (ALT) >3× upper limit of normal, which was observed in up to 3% of patients. However, further retrospective studies, clinical trial data, and post-market drug monitoring clarified that although transient transaminase elevations do occur, they were rarely clinically relevant. Furthermore, it is also unclear how much of

**Abbreviations:** AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ATV, atorvastatin; AUC, area under the curve; BCRP, breast cancer resistance protein aka ATP-binding cassette subfamily G member 2; C\(_{\text{max}}\), maximum concentration; CYP, cytochrome P450; DAA, direct-acting antiviral; DDI, drug-drug interaction; DILI, drug-induced liver injury; EtOH, alcoholic cirrhosis; FDA, US Food and Drug Administration; FLV, fluvastatin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; LOV, lovastatin; max, maximum; N/A, not available; NASH, nonalcoholic steatohepatitis; OATP, organic-anion-transporting polypeptide; Obs, retrospective observational trial; P-gp, P-glycoprotein; PIIV, pitavastatin; PRV, pravastatin; RCT, randomized clinical trial; ROS, rosuvastatin; SMV, simvastatin.

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the transient elevations in ALT are due to underlying non-alcoholic steatohepatitis (NASH), a potentially significant confounder. In a post hoc analysis of patients with abnormal transaminases in the Greek Atorvastatin and Coronary Heart Disease Evaluation study, atorvastatin (ATV) was associated with statistically significantly improved ALT levels compared with placebo (−35% vs +12%; P = 0.003).7

Of 1188 patients with drug-induced liver injury (DILI) evaluated by the DILI Network, just 22 (1.8%) were potentially attributable to statins.8 Among 1,198 cases of acute liver failure prospectively collected by the Acute Liver Failure Study Group, only 6 were attributable to statins (0.5%) and 2 of these were due to cervistatin,9 which was withdrawn from the market because of increased rhabdomyolysis incidence. It is difficult to estimate the total incidence of liver failure given the high prevalence of statin use and the low incidence of liver failure. One study placed the rate of ALF attributable to statins at 0.2 per million, which is a lower frequency than in the general population.10

In 2006, the National Lipid Association Statin Safety Task Force concluded that irreversible liver damage was exceptionally rare and likely idiosyncratic, and that routine serum liver test monitoring did not prevent these events.11 In 2012, the FDA approved safety label changes recommending against routine serum liver test monitoring in patients who are prescribed statins.12

It is worthwhile to note that there have been case reports of statins triggering autoimmune hepatitis (AIH), a phenomenon that has been observed by the authors as well. This is postulated to occur via induction of autoantibodies to biosimilar epitopes in genetically susceptible individuals. In published data, it has been observed to generally occur 2 to 7 months after statin initiation, can persist after the statin is discontinued, and responds similarly to standard AIH treatments including steroids, azathioprine, and mycophenolate.13-15 With such a low incidence, there are no changes to guidelines regarding increased monitoring or avoidance of statins even in patients with higher risk for autoimmunity.

PROSPECTIVE AND RETROSPECTIVE STUDIES REFUTE HEPATOTOXICITY CONCERNS IN PATIENTS WITH CHRONIC LIVER DISEASE

In patients with liver disease, the risk to patients from statins is more adequately described by looking separately at patients with chronic liver disease without cirrhosis, compensated cirrhosis, and decompensated cirrhosis. Lewis et al.16 published the singular prospective trial of statins in patients with chronic liver disease; most had non-alcoholic fatty liver disease (64%) or hepatitis C (23%). Patients receiving pravastatin (PRV) had noninferior rates of elevations in ALT (7.5% versus 12.5%; P = 0.139). In six retrospective cohort or propensity-score matching analyses in noncirrhotic liver disease, there was no increased incidence of hepatotoxicity (Table 1).17-22 Furthermore, recently proposed guidelines for treatment of hypercholesterolemia in primary biliary cholangitis similarly find little risk for hepatotoxicity with statin use prior to the development of cirrhosis.23

PHARMACOKINETICS OF STATINS ARE ALTERED IN CIRRHOSIS

Most statins are metabolized through the cytochrome P450 (CYP) system prior to biliary excretion, including lovastatin (LOV), simvastatin (SMV), and ATV. Furthermore, many are reliant on transport mechanisms such as organic-anion-transporting polypeptides (OATPs), P-glycoprotein (P-gp), and BCRP (aka ABCG2). Synthetic dysfunction in cirrhosis causes altered pharmacokinetics, measured in both maximum concentration (Cmax) and area under the curve (AUC). Although published data are incomplete, the greatest known concern is ATV in decompensated cirrhosis, showing an 11-fold and 16-fold increase in Cmax and AUC, respectively.24 Rosuvastatin (ROS) and PRV require minimal metabolization prior to biliary excretion, and thus have pharmacokinetics closer to baseline despite decreased liver function.

STATINS LARGELY REMAIN SAFE IN COMPENSATED CIRRHOSIS

In compensated cirrhosis, the preponderance of evidence shows that statins are still safe despite the change in pharmacokinetics. In four prospective randomized clinical trials (RCTs) with enrollment sizes of 23 to 158, there was no statistically significant increase in hepatotoxicity, and only one patient had to be taken off of the statin because of elevated transaminases.25-28 Similarly, there was no statistically significant increase in mild (diarrhea, myalgia) to severe (ascites, spontaneous bacterial peritonitis, and variceal hemorrhage) adverse events. In five retrospective studies with cohort sizes of 343 to 40,512, no increase in adverse events or mortality was noted.29-33 Meta-analysis shows that rather than
### Table 1. Prospective and Large Retrospective Studies on Statins in Patients with Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Year</th>
<th>Authors</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>Type of Statin</th>
<th>Etiology of Cirrhosis</th>
<th>Severity of Disease</th>
<th>Hepatotoxicity</th>
<th>Improvement With Statin in Progression of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>2009</td>
<td>Abraldes et al.</td>
<td>59</td>
<td>1</td>
<td>SMV</td>
<td>EIO/HBV/HCV</td>
<td>Decompensated cirrhosis</td>
<td>None</td>
<td>Yes (none)</td>
</tr>
<tr>
<td>RCT</td>
<td>2015</td>
<td>Pollo-Flores et al.</td>
<td>34</td>
<td>3</td>
<td>SMV</td>
<td>EIO/HBV/HCV</td>
<td>Decompensated cirrhosis</td>
<td>None</td>
<td>Yes (none)</td>
</tr>
<tr>
<td>RCT</td>
<td>2016</td>
<td>Abraldes et al.</td>
<td>158</td>
<td>12</td>
<td>SMV</td>
<td>EIO/HBV/NASH</td>
<td>Decompensated cirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>RCT</td>
<td>2018</td>
<td>Bishnu et al.</td>
<td>23</td>
<td>12</td>
<td>ATV</td>
<td>EIO/HBV/NASH</td>
<td>Decompensated cirrhosis</td>
<td>None</td>
<td>Yes (none)</td>
</tr>
<tr>
<td>Obs</td>
<td>2008</td>
<td>Avins et al.</td>
<td>93,106</td>
<td>29</td>
<td>LOV</td>
<td>EIO/HBV/HCV/NASH</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2014</td>
<td>Motzku-Floegons et al.</td>
<td>19,379</td>
<td>40</td>
<td>Mixed (90% SMV)</td>
<td>EIO/HBV/HCV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Not measured</td>
</tr>
<tr>
<td>Obs</td>
<td>2014</td>
<td>Kumar et al.</td>
<td>243</td>
<td>36</td>
<td>Mixed (49% SMV)</td>
<td>EIO/HBV/HCV/NASH</td>
<td>Mixed cirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2015</td>
<td>Hsiang et al.</td>
<td>77,021</td>
<td>20</td>
<td>Mixed (85% ATV/SMV)</td>
<td>HBV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Not measured</td>
</tr>
<tr>
<td>Obs</td>
<td>2015</td>
<td>Butt et al.</td>
<td>33,899</td>
<td>32</td>
<td>Mixed</td>
<td>HBV</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2015</td>
<td>Yang et al.</td>
<td>226,856</td>
<td>90</td>
<td>Mixed</td>
<td>HBV</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2015</td>
<td>Dongiovanni et al.</td>
<td>1,201</td>
<td>N/A</td>
<td>Mixed</td>
<td>NASH</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Not measured</td>
</tr>
<tr>
<td>Obs</td>
<td>2016</td>
<td>Mohanty et al.</td>
<td>40,512</td>
<td>30</td>
<td>Mixed (85% SMV)</td>
<td>HCV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2016</td>
<td>Oliver et al.</td>
<td>50985</td>
<td>74</td>
<td>Mixed</td>
<td>HCV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2016</td>
<td>Simon et al.</td>
<td>47,459</td>
<td>98</td>
<td>Mixed</td>
<td>HCV</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2016</td>
<td>Huang et al.</td>
<td>28,761</td>
<td>56</td>
<td>Mixed</td>
<td>HBV</td>
<td>Noncirrhosis</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Obs</td>
<td>2017</td>
<td>Bang et al.</td>
<td>24,748</td>
<td>67</td>
<td>Mixed</td>
<td>EIO/HBV/HCV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Not measured</td>
</tr>
<tr>
<td>Obs</td>
<td>2017</td>
<td>Chang et al.</td>
<td>15,931</td>
<td>66</td>
<td>Mixed</td>
<td>EIO/HBV/HCV</td>
<td>Compensated cirrhosis</td>
<td>None</td>
<td>Not measured</td>
</tr>
</tbody>
</table>
worsening of liver function, there was a statistically significant improvement in disease progression and mortality.34

**STATINS IN DECOMPENSATED CIRRHOSIS SHOULD BE APPROACHED WITH CAUTION**

In patients with decompensated cirrhosis, especially those with Child-Pugh class C cirrhosis, benefits are more limited, whereas the risks are increased. Prevention of progression of disease is difficult when the underlying disease is already in an advanced state. Given the grave prognosis of patients with Child-Pugh class C cirrhosis and time to benefit of statins, it is not surprising that the improvement in mortality seen in the 2016 study by Abraldes et al.25 was limited to patients with Child-Pugh class A and B cirrhosis.

Dose-dependent increased risk for rhabdomyolysis has been shown in patients without cirrhosis in an RCT of high-dose versus low-dose SMV (80 mg versus 20 mg daily), with an absolute increase of 0.77% in 12,064 patients.35 There is concern that as the pharmacokinetics of statins become more altered in advanced cirrhosis, there will be an increase in adverse events. Although data are limited, Abraldes et al.25 did note two patients to have symptomatic elevations in creatine kinase–muscle/brain. There were no other reports of this from three other prospective RCTs.26-28 There are currently no guidelines regarding the statin use in these populations, so a cautious approach with close monitoring should be encouraged if proceeding with therapy.

**DRUG-DRUG INTERACTIONS MAY REQUIRE STATIN DOSE ADJUSTMENTS OR DISCONTINUATION**

As understanding is gained of the transport and metabolism of each of the statins, it becomes possible to better predict which drug-drug interactions (DDIs) pose increased risk for altered pharmacokinetics and side effects. Hepatologists should be familiar with recommendations regarding coadministration of statins with direct-acting antivirals (DAAs) for hepatitis C and immunosuppression (Table 2).36-39 Although sofosbuvir (Sovaldi) does not interact with statins, the drugs with which it is most often paired have varying effects on the aforementioned pathways of statin transport and degradation. Cyclosporine has the most DDIs, and thus the most restrictions for coadministration with regard to statins. Fellow calcineurin inhibitor tacrolimus and the mammalian target of rapamycin inhibitors such as sirolimus and everolimus have lesser interactions and restrictions.40,41

**CONCLUSION**

Despite earlier concerns for hepatotoxicity, clinically relevant risks to the liver from statins remain remarkably low in patients without cirrhosis and should not outweigh the broad cardiovascular and potential hepatic benefits. As NASH becomes an increasingly common cause of cirrhosis and indication for transplant, the need for aggressive lipid and cardiovascular risk modification will only grow in importance.

In small prospective and large retrospective studies, statins were found to be safe in compensated cirrhosis (Table 1). In decompensated cirrhotics, decreased time for benefit and potential increased risk for rhabdomyolysis warrant caution in prescribing statins, preferably with the assistance of a hepatologist. Attention must always be paid to DDIs, especially with DAAs for hepatitis C treatment and immunosuppression in the posttransplant setting.

**TABLE 2. DRUG-DRUG INTERACTIONS WITH STATINS AND COMMONLY USED DRUGS IN HEPATOLOGY**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transport and Metabolism Pathways</th>
<th>Lowest Dose Necessary (Weak Interaction)</th>
<th>Dose Reduction (Moderate Interaction)</th>
<th>Hold Drug (Strong Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>OATP, P-gp, BCRP</td>
<td>ATV, FLV, LOV, PIV, SMV</td>
<td>N/A</td>
<td>ROS</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>OATP1B1/3, P-gp, BCRP</td>
<td>ATV, FLV, LOV, SMV</td>
<td>ROS (10 mg/day)</td>
<td>N/A</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir/voxilaprevir</td>
<td>OATP1B1–3, P-gp, BCRP, CYP-3A</td>
<td>ATV, FLV, SMV</td>
<td>PIV (max 40 mg/day)</td>
<td>ROS, PIV</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>OATP1B1/3, P-gp, BCRP, CYP-3A</td>
<td>FLV, PIV</td>
<td>PIV (max 20 mg/day), ROS (max 10 mg/day)</td>
<td>ATV, LOV, SMV</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>OATP1B1, P-gp, CYP-3A</td>
<td>FLV</td>
<td>ATV, PIV (max 20 mg/day), ROS (max 5 mg/day)</td>
<td>LOV, PIV, SMV</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>OATP1B1, P-gp, CYP-3A</td>
<td>ATV, FLV, PIV, ROS</td>
<td>ATV, PIV (max 20 mg/day), ROS (max 5 mg/day)</td>
<td>LOV, PIV, SMV</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>P-gp, CYP-3A</td>
<td>ATV, FLV, PIV, ROS</td>
<td>PIV (max 20 mg/day), ROS (max 5 mg/day), SMV</td>
<td>LOV, PIV, SMV</td>
</tr>
<tr>
<td>Everolimus</td>
<td>P-gp, CYP-3A</td>
<td>ATV, FLV, PIV, ROS</td>
<td>PIV (max 20 mg/day), ROS (max 5 mg/day), SMV</td>
<td>LOV, PIV, SMV</td>
</tr>
</tbody>
</table>
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