Treatment of Dyslipidemia in Common Liver Diseases

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Dyslipidemia is common in the general population and increases the risk of cardiovascular disease. Treatment of dyslipidemia is effective in decreasing morbidity from cardiovascular disease. Because the liver is the primary source of cholesterol and other lipids in the body, medications for dyslipidemia, such as statins, target genes in the liver. Furthermore, the liver plays a role in the metabolism of many drugs, including those that are used to treat dyslipidemia. It is not surprising, therefore, that many practitioners are hesitant to prescribe medicines to treat dyslipidemia in the setting of liver disease. This update is aimed at summarizing current understanding of the safety of treating patients who have various liver diseases and dyslipidemia with lipid-lowering drugs.

The 2013 American College of Cardiology/American Heart Association guidelines, published in 2014, should be used to guide treatment of dyslipidemia in patients with the liver diseases discussed in this update.[1] The guidelines recommend that adults with cardiovascular disease or a low-density lipoprotein (LDL) level $\geq$190 mg/dL be treated with high-intensity statins, with the goal of reducing LDL levels by 50%. Individuals 45–70 years of age with diabetes mellitus and a serum LDL level $<$189 mg/dL or persons with a $>$7.5% global 10-year risk of cardiovascular disease can be treated with moderate-intensity statins, with the goal of reducing LDL levels by 30%–50% (Table 2).

Drug-Induced Liver Injury

From 8% to 9% of persons in the general population have an elevated aminotransferase level, a common clinical problem.[2] In these persons, an evaluation to determine the cause of the aminotransferase elevation is warranted, particularly before a new drug is started, because they may have a common underdiagnosed condition, such as nonalcoholic fatty liver disease (NAFLD), excessive alcohol use, or viral hepatitis. Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) are by far the most common medication used to treat dyslipidemia and are known to cause elevations of serum alanine aminotransferase (ALT) levels in persons with previously normal levels. Overall, persons on low-to-moderate statin doses have, on average, a 1% chance of having an elevated ALT level.[3] At most, 3% of patients on statins develop elevations in serum ALT levels.[3] The effect is generally dose dependent, with higher doses of statins increasing the chances of an elevated ALT level. These mild elevations do not generally indicate serious toxicity.

Elevations in aminotransferase level indicative of serious liver injury caused by a drug are rare but can be life threatening. Zimmermann[4,5] observed that jaundiced patients with elevated aminotransferase levels had a poorer prognosis than patients with elevated aminotransferase levels without jaundice. That observation was further developed into Hy's Law to identify patients with potentially fatal drug-induced liver injury (DILI).[6] To meet criteria for DILI, patients must have elevations of ALT or aspartate aminotransferase levels $\geq$3 times the upper limit of normal (ULN) and have elevations of the total serum bilirubin level $>$2 times the ULN with no other identified cause of the increased liver biochemical tests (eg, biliary obstruction, another liver disease, other drug toxicity) except for the offending drug.[6] DILI from statins occurs in 1 in 100,000 persons and can have a variety of histologic presentations.[7,8] There can be an asymptomatic rise in the ALT level ($<$3 times ULN) that can improve with continued stain use, so-called adaptation; hepatitis with an ALT level $>$3 times ULN and clinical liver disease; cholestatic hepatitis with development of jaundice; and autoantibody-associated DILI with the development of positive antinuclear antibodies and antimitochondrial or smooth muscle antibodies with or without plasma cells in liver biopsy specimens. In general, however, statins can be used in individuals with autoimmune disorders including autoimmune hepatitis. General care should be taken to ensure that medications taken for autoimmune hepatitis or other disorders do not affect the catabolism or excretion of statins, thereby altering their effective dose. Statins can also cause acute liver failure in 1 in 1,000,000 persons.

Abbreviations used in this paper: **ALT, alanine aminotransferase; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; RCT, randomized controlled trial; ULN, upper limit of normal.**

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Table 1. Best Practice Advice: Treatment of Dyslipidemia in Liver Disease

DILI

BPA #1 Statins often (3%) cause benign elevations in serum ALT or AST levels and should not be considered contraindicated in patients with liver disease.

BPA #2 Liver biochemical tests are recommended before starting a statin but do not need to be checked routinely while statins are taken unless clinically significant side effects develop.

BPA #3 Increases in serum ALT or AST levels to >3 times ULN with evidence of cholestasis (bilirubin >2 times ULN) (in the absence of biliary obstruction) after statins are started generally require that the statin be stopped. A work-up for DILI should include testing for the presence of other underlying causes of liver disease or other medications that may have precipitated the reaction besides or in addition to the statin.

BPA #4 If DILI or ALF occurs in a patient taking a statin, other statins should be avoided in that patient.

BPA #5 DILI and ALF caused by statins are rare (1 in 100,000 and 1 in 1,000,000, respectively), so fear of developing these effects should not be used to justify avoidance of statins when an individual may benefit from them.

BPA #6 Statins are contraindicated in patients with ALF because of the patients' poor prognosis.

BPA #7 Other lipid-lowering medications, such as niacin, ezetimibe, or fibrates, may cause DILI, but such instances are exceedingly rare and should not prevent starting these medications in a patient who may benefit from them.

NAFLD

BPA #8 Although NAFLD and NASH are not considered traditional risk factors for cardiovascular disease, they are associated with dyslipidemia. The 2013 ACC/AHA guidelines should be used to assess cardiovascular risk in patients with NAFLD and to guide the need for lipid-lowering pharmacotherapy.

BPA #9 Statins, ezetimibe, omega-3 fatty acids, and fibrates are safe and well tolerated in the setting of NAFLD and NASH.

BPA #10 A statin is first-line treatment of elevated serum LDL levels in patients with NAFLD who are deemed to be at increased risk for adverse cardiovascular disease outcomes. Statin therapy is associated with reductions in serum LDL levels and cardiovascular disease prevention in patients with NAFLD.

BPA #11 Ezetimibe may also be used for treatment of elevated LDL levels, either as primary therapy in patients who are statin intolerant or in addition to a statin when the statin is insufficient to reduce LDL levels. Ezetimibe is associated with reductions in LDL levels, but its efficacy for cardiovascular disease prevention is unknown.

BPA #12 Omega-3 fatty acids and fibrates are indicated for the treatment of isolated hypertriglyceridemia.

BPA #13 There is no conclusive evidence that treatment of dyslipidemia with any agent (statin, fibrate, fish oil) improves the histology of NASH or liver-related outcomes.

Viral Hepatitis

BPA #14 Despite causing a reduction in serum lipid levels, chronic HCV infection is associated with an increased risk of acute myocardial infarction. Serum LDL and total cholesterol levels rebound after spontaneous and treatment-induced viral clearance. Therefore, lipid levels should be monitored after HCV clearance to determine if a patient has a new indication for treatment of dyslipidemia.

BPA #15 The impact of chronic HBV infection on serum lipid levels is not well described, but HBV infection may decrease serum triglyceride and HDL levels.

Table 1. Continued

BPA #16 Management of patients with HBV or HCV infection and dyslipidemia should be guided by standard recommendations for the treatment of dyslipidemia.

BPA #17 Statins are safe to use in patients with either chronic HCV or HBV infection, but attention should be paid to potential interactions between statins and antiviral agents.

PBC

BPA #18 Dyslipidemia in the form of elevated serum cholesterol and triglyceride levels is common in PBC, does not increase the risk of cardiovascular disease, and does not need to be treated with lipid-lowering agents unless other concomitant cardiovascular risk factors are present.

BPA #19 Lipid-lowering agents, such as statins, are not contraindicated in patients with PBC with compensated liver disease but should not be used in patients with decompensated disease.

BPA #20 Second-line treatments for PBC, such as fibrates and OCA, can affect lipid levels. Until more is known about the effect of OCA on cardiovascular disease, OCA in particular should be avoided in patients with PBC who have cardiovascular disease or risk factors for disease. OCA should be dosed weekly rather than daily in PBC patients with Child-Pugh class B or C cirrhosis.

BPA #21 There is no compelling evidence that statins can improve outcomes in patients with PBC; they should not be used as primary agents for treatment of this disease.

Cirrhosis

BPA #22 Statins can be safely used in patients with Child-Pugh class A cirrhosis for cardiovascular risk reduction if indicated.

BPA #23 Statins should be avoided in patients with Child-Pugh class B or C cirrhosis because of the patients' poor prognosis, not because of increased hepatotoxicity.

Post-Transplant Dyslipidemia

BPA #24 Dyslipidemia is common following liver transplantation, affecting up to 62% of transplant recipients. Pretransplant obesity and diabetes mellitus increase the risk of post-transplant dyslipidemia. Post-transplant weight gain and immunosuppressant medications, including calcineurin inhibitors and the mTOR inhibitor sirolimus, also increase the risk of post-transplant dyslipidemia.

BPA #25 Lipid-lowering agents, specifically statins, are not associated with an increased risk of hepatotoxicity in the post-transplant population and may be used as needed to treat dyslipidemia.

BPA #26 Calcineurin inhibitors, like several statins, are metabolized by CYP3A4 and may increase the risk of statin-associated myopathy. Pravastatin and fluvastatin are not metabolized by CYP3A4 and do not increase the risk of statin-associated myopathy when used with a calcineurin inhibitor.

ALT, alanine aminotransferase; ACC, American College of Cardiology; AHA, American Heart Association; ALF, acute liver failure; AST, alanine aminotransferase; BPA, best practice advice; CYP, cytochrome P-450; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mTOR, mechanistic target of rapamycin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PBC, primary biliary cholangitis; ULN, upper limit of normal.

The liver safety of statins has recently been reviewed and guidelines published for their use.[9] It is recommended that liver biochemical tests be checked before a statin is started. However, routine periodic monitoring of serum ALT levels does not seem to detect or prevent