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Controlling Statin Effects on Liver Diseases by Enzymes Alterations

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ABSTRACT

Statins are widely used to reduce cardiovascular risk, but their safety in patients with liver diseases requires careful evaluation. In the general population, 1% to 3% of users may present elevated aspartato aminotransferase (AST) levels, though severe liver injury from statins is rare. Statins should not be discontinued for alanine aminotransferase (ALT) elevations under three times the upper limit of normal, but must be stopped if this limit is exceeded alongside increased bilirubin. Routine ALT monitoring is not recommended unless symptoms like fatigue or jaundice occur. Statins are contraindicated in decompensated liver disease but considered safe in compensated liver conditions. In patients with metabolic dysfunction-associated steatotic liver disease (MASLD), statins are first-line therapy to control atherogenic dyslipidemia and reduce cardiovascular morbidity and mortality. They may also decrease liver fibrosis progression and reduce overall mortality and the risk of hepatocellular carcinoma. Other agents like fibrates and Omega 3 can complement therapy. In chronic hepatitis B and C, statins do not worsen liver damage and may improve enzyme profiles. In compensated primary biliary cholangitis, statins can be used, though they are not effective in reducing cholestasis markers. Ezetimibe is also considered safe in these cases. Statins are safe for patients with Child-Pugh class A cirrhosis but should be avoided in classes B and C due to increased risk of adverse effects. Preliminary studies suggest statins may reduce hepatocellular carcinoma risk, but more randomized trials are needed to confirm these findings.

Keywords: Statins; Hepatitis; Transferases; Cirrhosis; Adverse Effects

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; MASLD: Metabolic Dysfunction Associated Steatotic Liver Disease; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis

Introduction

It is of fundamental importance to monitor possible side effects in patients who are prescribed chronic use of a new drug, especially when they already have previous dysfunctions [1]. In the present study, the question was restricted to the effect of statins in patients with liver diseases, following the specific enzymatic variations for this. In the general population, 1% to 3% of individuals using statins develop elevations in serum aspartate aminotransferase (AST) levels [2]. There are data suggest that individuals with elevated liver enzymes do not have increased susceptibility to hepatotoxicity from statins [3]. The prevalence of severe statin-induced liver injury is 1 in 100,000 individuals and acute liver failure is 1 in 1,000,000 individuals [4].

- **Patients with statin-induced acute liver injury present:** Elevations of alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal and elevation of total bilirubin > 2 times the upper limit of normal, with no other cause identified [4].
- **Hepatic safety of statins:** Liver evaluation with laboratory tests should be done prior to initiation of statin use.

- **Periodic monitoring:** Routine measurement of ALT levels does not seem to detect or prevent serious liver damage associated with statin use, and is not recommended [4]. Measurement of the complete hepatic profile in patients taking statins should be done in the presence of recurrent nausea, fatigue, fever, or jaundice. If a patient has experienced acute liver injury caused by statins, this class of drugs should not be recommended again. Statins are contraindicated in patients with decompensated liver disease or acute liver failure, and are safe in lowering lipid levels in patients with compensated liver disease [2].
- **Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as hepatic steatosis in adults who have at least one cardiometabolic risk factor:** Overweight/obesity, type 2 diabetes, prediabetes, systemic arterial hypertension, or atherogenic dyslipidemia, in the absence of secondary causes [5].
- **Cardiovascular prevalence and risk:** It is highly prevalent and associated with increased risk of major cardiovascular events.
- **Reduction of cardiovascular risk:** It is necessary to treat the comorbidities associated with MASLD such as systemic arterial hypertension, diabetes mellitus, obesity and dyslipidemia [5]. Statins are the first choice because they treat the atherogenic dyslipidemia present in MASLD, in addition to reducing morbidity and mortality due to atherosclerotic cardiovascular disease in these patients. Other lipid-lowering agents such as fibrates and Omega 3 fatty acids can help statins in the treatment of mixed dyslipidemias, which is common in these patients [6].
- **Liver outcomes:** A cohort study demonstrated that statins in the MASDL reduced the risk of all-cause mortality, hepatic decompensation, and hepatocellular carcinoma [6]. Statin use has also been associated with reduced progression of liver stiffness, an indicator of fibrosis progression, in both patients with and without advanced chronic liver disease [7]. Meta-analyses and systematic reviews indicate that statins can improve liver function tests, decrease the degree of steatosis and fibrosis in statin users, probably mediated by anti-inflammatory and antifibrotic mechanisms [6].
- **Safety:** Statins should not be withheld in patients with stable chronic liver disease and normal or modestly elevated transaminases (up to three times the upper limit of normal) as they do not cause progression of liver disease. In these patients, liver function tests should be monitored periodically [8].

Hepatitis B e C

Statin therapy does not increase AST levels or liver damage in hepatitis B and C patients, and some evidence suggests it may slightly improve liver enzyme measurements. Recent studies do not report evidence of statin-induced hepatotoxicity. The findings indicate that statin therapy does not exacerbate liver damage - as measured by AST - and may be associated with modest improvements in liver enzyme profiles in patients with chronic viral hepatitis [9-11].

Intra-Hepatic Cholestasis

Primary biliary cholangitis is an autoimmune cholestatic liver disease, characterized by chronic inflammation associated with dyslipidemia [12]. Elevated total cholesterol levels largely occur due to elevations of lipoprotein X, which is not atherogenic and does not impact cardiovascular risk. The use of lipid-lowering drugs is indicated in the presence of factors that contribute to increased cardiovascular risk in this population. Statins are not contraindicated in primary biliary cholangitis patients with compensated liver disease, but should not be used in decompensated liver disease [13]. There is no evidence of the effect of statins on reducing markers of intrahepatic cholestasis in primary biliary cholangitis [13]. Studies have shown safety with the use of ezetimibe in patients with primary biliary cholangitis and associated with statins should be considered in patients with primary biliary cholangitis with risk factors for cardiovascular diseases [12].

Cirrhosis of the liver

Although cirrhosis was thought to protect against atherosclerotic disease, it is known that the prevalence of coronary artery disease in patients with cirrhosis may be higher than in the general population. Cardiovascular risk varies according to the etiology of liver disease and is higher in cirrhosis caused by alcohol, hepatitis C virus (HCV), and nonalcoholic steatohepatitis (NASH) [14]. Statins are safe and can be used in patients with Child-Pugh class A cirrhosis [14]. In Child-Pugh class B or C cirrhosis, the use is not recommended, because moderate to severe hepatic insufficiency reduces the metabolism of the drug, raising its serum levels, which predisposes to adverse effects [14]. Evidence of the benefits of statins in reducing portal hypertension and hepatic decompensation in patients with cirrhosis is scarce, and it is not indicated for this treatment purpose [14]. The impact of statins on liver outcomes in patients with cirrhosis is being evaluated in ongoing randomized trials.

Hepatocellular Carcinoma

Case-control studies, predominantly conducted in cohorts of patients with viral hepatitis, demonstrated a 25% reduction in the incidence of hepatocellular carcinoma in the group exposed to lipophilic statins compared to those not exposed [14]. Meta-analyses suggest that statin therapy is associated with reduced incidence of hepatocellular carcinoma, but prospective randomized data are needed.

Conclusion

It is not recommended to discontinue statins when there is an increase in ALT less than three times the upper limit of normality, with strong recommendation and strong scientific evidence. In cases where the increase in ALT exceeds three times the upper limit

of normality, the suspension of statins is recommended, also with strong recommendation and strong evidence. Statins, fibrates, ezetimibe, and omega 3 are indicated for the treatment of dyslipidemias associated with MASLD, with strong recommendation and moderate evidence. Among these drugs, statins stand out as those that effectively reduce cardiovascular risk in patients with MASLD, with strong recommendation and strong evidence. In the context of compensated primary biliary cholangitis, statins are indicated for the treatment of dyslipidemia, while their use is contraindicated in cases of the same disease with changes in liver function. These guidelines have weak recommendations and weak evidence. In patients with liver cirrhosis, statins are considered safe and can be used in those classified as Child-Pugh class A, with moderate recommendation and weak evidence. However, in cases of Child-Pugh class B or C cirrhosis, the use of statins is discouraged, maintaining the same strength of recommendation and evidence.

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None.

Conflict of Interest

None.

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