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Editorial

Statins and Hepatotoxicity

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Since 1987, statins are among the most widely prescribed medications for primary and secondary prevention of cardiovascular disease around the world. Numerous clinical trials and extensive clinical experience have established that currently available statins have an excellent safety profile.[1,2] Asymptomatic elevations in liver enzymes are common in patients treated with statins due to a pharmacodynamic effect of lipid lowering, but clinically significant liver injury is extremely rare. The incidence of significant elevation in alanine aminotransferase levels (>3 times upper limit of normal on two or more measurements) is dose-related and generally less than 3%.[3] These asymptomatic aminotransferase elevations may occur in all lipid lowering agents including ezetimide which has no effect on liver metabolism and could be caused by changes in hepatocyte membrane composition.

Due to the information contained in the package inserts about potential hepatotoxicity in everyday clinical practice there is often a question about the elevation of liver enzymes in treated patients. In a recent meta-analysis that consisted of 49,275 patients who participated in 13 large, placebo-controlled trials, therapy with statins at low-to-moderate doses was not associated with a significant increase in liver enzyme elevations compared to placebo.[4] Significant liver injury (hepatocellular, cholestatic or mixed) associated with statins, due to idiosyncratic or immunoallergic mechanisms, appears to be very rare.[5] Generally speaking, idiosyncratic drug-induced liver injury occurs in a very small subset of treated individuals and patients with chronic liver disease are not at higher risk.[6,7] Most individuals who experience mild to moderate aminotransferase elevations can adapt to and are not at risk of developing significant liver injury despite continuous use of the drug. Fulminant liver failure attributable to lovastatin was estimated to be 2 in one million patients.[8] In another review, the incidence of statin associated liver failure was found to be 1 per million person-years of use.[1] There are no identified risk factors that increase the frequency of clinically significant statin hepatotoxicity. Genetic polymorphism in metabolic pathways may be an important factor in determining which individuals are susceptible to severe adverse drug reaction.[9,10] Furthermore, there is no evidence that statin interaction with fibrates plays a role in liver injury such as causing myopathy and rabdomyolysis.[3]

The presence of NAFLD may portray a higher cardiovascular risk necessitating statin therapy.[11,12,13] On the other hand, there is often a concern about the safety of prescribing statins in individuals with asymptomatic liver enzyme elevations, due to alcoholic and non-alcoholic liver disease-NAFLD, hepatitis C virus infection (HCV), other drugs etc. Many hyperlipidemic individuals with elevated baseline liver enzymes have increases in their liver enzymes whether or not they receive statins.[14] Nevertheless, hyperlipidemic individuals with baseline elevated liver enzymes did not have a higher frequency of statin hepatotoxicity than those with normal liver enzymes.[15] Moreover, statins given to patients with non-alcoholic steatohepatitis are well tolerated[16] and some patients exhibited significant improvement in hepatic biochemistry and histology.[17,18,19]

A panel of hepatologists, providing advice to the American National Lipid Association's safety task force regarding statin safety, discouraged routine liver biochemistry monitoring in asymptomatic individuals no matter the aminotransferase increase.[20] Routine monitoring of treated people will identify patients with isolated increased liver enzymes which could lead the physician in charge to discontinue therapy inappropriately. When the practicing

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physician is concerned about the possible occurrence of a hepatotoxic reaction to statin therapy (because the patient reports fatigue, malaise, lethargy, jaundice etc) an assessment of the fractionated bilirubin level is advisable. Bilirubin levels are the most reliable prognosticators of liver injury in the setting of drug toxicity.[21]

The existing data provide evidence that statins can be used safely in patients NAFLD. More studies should be conducted to evaluate the long-term effects of statins on hepatic histology in patients with NAFLD. Moreover, statins may afford a future therapeutic strategy for the treatment of HCV infection. In cultured hepatoma cells, HCV RNA replication was disrupted by treatment with lovastatin, which induced the dissolution of the HCV replication complex.[22] Additionally, statins appear to be promising adjunctive anticancer drugs for management of hepatocellular carcinoma.[23]

In conclusion, the current recommendation that liver biochemistries be checked before and periodically after starting statin therapy is not evidence based.[24] There is no sound rationale why statins should not be used in patients with compensated chronic liver diseases (including cirrhosis) who otherwise need hypolipidemic therapy. This recommendation needs to be reexamined by the manufacturers and regulatory agency. Decompensated liver cirrhosis or acute liver failure should remain an absolute contraindication for statin therapy.

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