Conference Report

Pharmacotherapy in Cirrhosis

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The prevalence of chronic liver disease is on the rise worldwide. Along with it comes an increase in patients who have liver cirrhosis and its complications. Hepatocellular carcinoma (HCC) is one of the complications of cirrhosis. Approximately half a million new cases of hepatocellular carcinoma are diagnosed worldwide on an annual basis.[(1)] While chronic viral hepatitis B and C still account for the majority of these cases, NASH-related end stage liver disease is on the rise and calculated to surpass both viral diseases in causing liver cirrhosis, HCC and liver-related deaths.

There are multiple considerations when managing the medications that patients with chronic liver diseases and with liver cirrhosis are exposed to.[(2)] Some drugs have decrease clearance or binding to albumin in cirrhosis and inadequate dosing may lead to drug-induced liver injury (DILI). Recent examples are NS5a protease inhibitors and Obeticholic acid. In patients with liver cirrhosis, medications more commonly cause acute kidney injury, GI bleeding and hepatic encephalopathy than DILI.

The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in patients with chronic liver disease has been controversial in the USA. Primary care physicians have been concerned about possible statin-induced hepatotoxicity. According to *Janicko et al*.[(3)] there are 1.2 cases of statin-DILI per 100,000 users with highest rates reported with Fluvastatin and lowest with Pravastatin. Simultaneously, about 2.7% of statin users will have mild asymptomatic transaminitis. An analysis of 1,188 cases of statin-DILI entered into the US national registry[(4)] concluded that

"Statin DILI is usually mild-to-moderate in severity and fairly rapidly reversed in most cases once the agent is stopped".

In the population of US Veterans chronically infected with hepatitis C virus and treated in the Veterans Administration system, not just statin use but dosing for 6 months or longer has been found to reduce the progression of liver fibrosis and the incidence of HCC in a statistically significant fashion.[5]

Similarly, in Taiwan, statin use was associated with a decreased risk of progression to liver cirrhosis in patients infected with hepatitis B and C viruses[6-7] and with a decreased risk of decompensation of liver disease in patients that had cirrhosis from chronic hepatitis B and C. [8]

Statins have been associated with increased survival in patients with liver cirrhosis. A study from Spain[9] looked at the effect of statins on bleeding from esophageal varices. Fifty percent of the study population were patients with alcohol-induced liver cirrhosis. The patients were randomized 1:1 to receiving Simvastatin or placebo starting 5-10 days after the index variceal bleed and were followed for 2 years. While the investigators found no difference in rates of rebleeding, the 2 years survival was statistically significantly better in those who received Simvastatin vs those who received placebo (22% vs 9%, respectively, p=0.03).

The benefit of statin therapy has recently been proposed in patients with yet a different type of chronic liver disease. [10] Registry data was analyzed for a population-based cohort of 2914 patients in Sweden affected with Primary Sclerosing Cholangitis (PSC) and concomitant Inflammatory Bowel Disease. 13.9% of these patients received statins. Statin use was associated with a reduced risk of all-cause mortality (hazard ratio [HR] 0.68; 95% CI, 0.54-0.88) and a 50% reduction in death or liver transplantation (HR, 0.50; 95% CI, 0.38-0.66). The risk of hepatobiliary cancer was not affected by statin use.

The risk vs benefit ratio as to whether to use statins in patients with chronic liver diseases with or without cirrhosis will probably favor the use of these medications. The next question then will be: Which statin should we use?

Simon and colleagues[11] set out to assess the relationship between lipophilic or hydrophilic statin use and HCC incidence and mortality in a Sweden nation-wide adult population infected with viral hepatitis B or C who filled a first (new user) prescription for a statin drug in between July 2005 and December 2013. Statin exposure in the Swedish registry population was limited to Simvastatin, Atorvastatin, Pravastatin and Rosuvastatin. Compared to statin non-users, lipophilic

(Simvastatin and Atorvastatin) statin users had significantly lower 10-year cumulative incidence of HCC (8.1% vs 3.3%; 95% CI, 0.41-0.79) but hydrophilic statin (Pravastatin and Rosuvastatin) users had no HCC incidence reduction benefit. In stratified models the relationships between statin type and HCC incidence were similar across all pre-specified subgroups, including sex, cirrhosis status and antiviral therapy use. Both, lipophilic and hydrophilic statin users had statistically lower 10-year all-cause mortality compared to non-users (15.2% vs. 7.3% for lipophilic statin users and 16.0% vs 11.5% for hydrophilic statin users). Lipophilic statin users but not hydrophilic statin users had significantly lower liver-specific mortality when compared to their non-users controls.

In conclusion, while the prevalence of chronic liver disease and the incidence of hepatocellular carcinoma are on the rise worldwide, there is data across different etiologies of chronic liver disease that strongly suggests that use of statins (maybe preferably lipophilic statins) may reduce the risk of developing HCC and liver-related and all-cause mortality in these patients.

References

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