Metformin and Statins and their role in reducing Hepatocellular Carcinoma Risk: Randomized trials are needed

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Hepatitis C infection has been a leading cause of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) for decades. At its peak, hepatitis C infected 170 million individuals worldwide. In Asia, hepatitis C along with hepatitis B are the driving forces behind the development of hepatocellular cancer(1). Therapies for hepatitis C have represented one of the major success stories in the history of medicine. From the discovery and identification of a transmissible agent in injection drug users, the observation that a finite course of interferon could normalize liver tests, to the development of direct-acting antiviral agents (DAAs) that lead to high rates of sustained virologic response (SVR), that is cure; few diseases have experienced such a rapid successful transition to a curable disease(2). Moreover, hepatitis C-related cirrhosis with or without HCC was previously the leading indication for liver transplantation, and recurrent hepatitis C post-transplantation remained a vexing problem with progression to cirrhosis occurring sometimes within 1-year post-transplant in the setting of immunosuppression(3). Those who achieve sustained response have a reduced risk of hepatocellular carcinoma, with that risk being reduced by approximately 70% in those with cirrhosis compared to those who do not achieve sustained response(4). Those who fail to achieve SVR are at higher risk for disease progression including fibrosis, cirrhosis, and hepatocellular cancer. Moreover, hepatitis C is associated with diabetes and other metabolic complications contributing to hepatic disease progression and development of HCC(5) (6). In the treatment of metabolic complications, numerous classes of medicines with pleiotropic effects improve insulin resistance, address hyperlipidemia, and have been associated with reduced risk of hepatocellular carcinoma. Indeed aspirin, statins, and antidiabetic agents including metformin and recently GLP-1 receptor agonists have all been associated with reduced risk of hepatocellular carcinoma(7-10).

Tsai and colleagues in this issue of Clinical Molecular Hepatology report in a cohort of HCV-infected individuals who have failed interferon-based therapies that those who received metformin
and statins for diabetes and hyperlipidemia have reduced risk of development of HCC compared to individuals with diabetes and hyperlipidemia not receiving these therapies (11). In this cohort from Taiwan (T-COACH cohort), 2779 chronic hepatitis C patients who failed interferon therapy were enrolled in a large cohort study and complications including HCC were monitored from 2003 to 2019. In multivariate analysis, factors associated with increased HCC risk included liver cirrhosis, age > 65, genotype 1, and diabetes mellitus without metformin use. In addition, patients with hyperlipidemia on statins had a significantly lower incidence of hepatocellular carcinoma than those with hyperlipidemia who were not taking statins. Aspirin use also lowered hepatocellular carcinoma risk.

Metformin users were defined as those with exposure 6 months after end of treatment (EOT) and statin users were defined similarly. In patients without liver cirrhosis, those with diabetes taking metformin had the lowest 5-year cumulative incidence rate of HCC at 3% compared to those without diabetes, and metformin non-users at 9.2% and 13.5% respectively. The risk of HCC was significantly higher in diabetic non-metformin users compared to non-diabetics (adjusted sub-distribution hazard ratio, aSHR, 1.73, P = 0.001) and higher than diabetics receiving metformin (aSHR 1.71, P = 0.014). In patients with cirrhosis, there were similar findings with metformin users having the lowest 5-year cumulative incidence of HCC at 3.6% compared to 23.3% in non-diabetics and 25.1%, in metformin non-users respectively though no difference in risk of HCC was noted between metformin non-users and the other groups.

Among patients on statins, similar patterns were observed. In patients without cirrhosis, the 5-year cumulative incidence rates of HCC were 10.4% in patients without hyperlipidemia, 3.1% in hyperlipidemia statin users, and 6.1% in hyperlipidemia statin non-users. HCC risk was significantly lower in hyperlipidemic statin users than in patients without hyperlipidemia (aSHR
0.43, P < 0.001) with no differences noted between hyperlipidemic statin users and hyperlipidemic statin non-users. Finally, in those with cirrhosis, those with hyperlipidemia on statins had a lower 5-year incidence of HCC (8.4%) as compared to those without hyperlipidemia (22.8%) and non-statin users (30.5%) with significantly lower risk of HCC in statin users compared to those without hyperlipidemia and non-statin users (aSHR 0.47 and 0.35 respectively). No differences in HCC risk were noted between patients without hyperlipidemia and hyperlipidemic patients not on statins.

The authors also conducted multiple sensitivity analyses. When redefining metformin and statin use as before and after EOT, they noted HCC risk remains significantly higher in diabetic metformin non-users than in diabetic metformin users (aSHR 2.28). A similar pattern was observed in those on statins before or after EOT with the risk of HCC remaining lower in patients with hyperlipidemia on statins than in those without hyperlipidemia. When the presence of advanced fibrosis (FIB-4>3.25) was considered, diabetic metformin non-users retained a higher risk of HCC compared to diabetic metformin users (aSHR = 1.54, P = 0.005) and there was a reduced HCC risk in statin users compared to those without hyperlipidemia (aSHR = 0.47, P < 0.001). These results persisted after excluding those retreated with DAA therapy, as well as those with reduced renal function (eGFR <30 ml/min) from the analysis. There were no significant differences in HCC risk between metformin nonusers and metformin users both among statin nonusers and statin users indicating no significant interaction between these medicine classes.

The data derived from this paper is from a unique cohort that likely will not be replicated again given the high efficacy and increasing access to DAA therapies for hepatitis C infection. This paper contributes to a growing literature of observational data that suggests that there may be chemopreventive options for those with liver disease and metabolic complications who are at risk for hepatocellular carcinoma. Both metformin and the statin class, particularly the lipophilic
class, have been reported to reduce the risk of incident hepatocellular carcinoma in broad population liver disease patients with metabolic complications(12). In addition, aspirin through anti-inflammatory mechanisms, and most recently GLP-1 receptor agonists in those with diabetes have also been shown to lower the risk of development of hepatocellular carcinoma in patients with chronic liver disease. However, those who fail interferon therapy for hepatitis C represent a class of chronic liver disease patients with active inflammation via multiple postulated pathways including classic pathogen pattern recognition, inflammasome activation, an intrahepatic inflammatory cascade response, and oxidative and endoplasmic reticulum stress(13). The mechanisms by which metformin reduces liver cancer risk are not yet precisely defined. Reduction of insulin levels, activation of adenosine monophosphate-activated protein kinase (AMPK) to reduce hepatic gluconeogenesis, inhibition of the mammalian target of rapamycin (mTOR) pathway and anti-inflammatory effects are all postulated mechanisms(14). Similarly, statins have pleiotropic effects including inhibition of HMG Co-A reductase to modify cell membranes, anti-inflammatory effects, promotion of apoptosis, inhibition of cell growth, and immune modulation which may all mitigate the risk of development of hepatocellular carcinoma(15).

There are limitations to observational studies including the report by Tsai and colleagues, which include the risks of selection bias, immortal time bias, and other confounding factors. To address these limitations, and confirm the benefit of these agents, multi-center adequately powered prospective trials should be conducted in populations at risk for HCC. Although the population of non-responders to hepatitis C therapy is no longer a major population, there remains a large population of patients with cirrhosis and diabetes who would potentially benefit from agents such as metformin, if demonstrated to reduce the risk of HCC. Given that those with cirrhosis are at the highest risk for the development of HCC, this population should be enrolled to ensure sufficient HCC events. The safety of metformin in compensated cirrhosis is well established, though
concerns of metformin-associated lactic acidosis remain in those with moderate or severe hepatic impairment and in those with reduced renal function (16). A similar approach may be used to study the role of statins in preventing HCC in those with cirrhosis. A pilot trial (NCT02968810) is assessing simvastatin to reduce disease progression from liver cirrhosis to cancer. Indeed, statins may also be associated with reductions in hepatic decompensation and the benefits in those with advanced liver disease will also be important to define. In addition, the safety of these agents can also be confirmed in prospective trials given that statins may raise ALT levels, lead to myopathy and muscle cramps, and are rarely associated with clinically significant liver injury (17). The paper by Tsai contributes to the growing literature suggesting that prospective evaluation of metformin and statins are required to address their potential benefit in our growing population of patients at risk for the development of hepatocellular carcinoma including those patients with hepatitis C and other chronic liver diseases.
REFERENCES


