Editorial

Hepatocellular carcinoma chemoprevention in chronic hepatitis B patients: all-in on statins?

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Chronic hepatitis B (CHB) affects approximately 257 million individuals worldwide, the highest prevalence being in Western Pacific WHO Region [6.2% (1)]. In highly endemic CHB regions, the 5-year cumulative incidence of hepatocellular carcinoma (HCC) ranges from 3% to 17%, depending on the presence of cirrhosis (2). Antiviral treatment decreases the risk of HCC, without abolishing it completely (3). Paradoxically, by decreasing liver-related mortality, antiviral treatment in CHB patients causes an increase in HCC long-term incidence (4).

Thus, prevention of HCC development in high-risk patients is theoretically an impactful strategy to improve patient prognosis. However, no such therapy has been established to date, despite some promising candidates. Diverse molecules such as aspirin, metformin, caffeine, anti-fibrotic therapies and statins have shown decreased hazard-ratios (HR) of HCC in high-risk populations (5).

The rationale behind statins use to prevent cancer lies in the biological pathways implicated in the response to statins. In experimental HCC models, statins showed inhibition of proto-oncogene Myc (6), AKT phosphorylation (7), nuclear factor-κβ (NFκβ) and tumour necrosis factor (TNF)-mediated interleukin 6 production (8). Numerous (and heterogeneous) observational studies on statins have suggested a decrease in HCC incidence in different settings of chronic liver disease. A meta-analysis (9) published in 2013 estimated a 41% decrease in HCC incidence in patients treated with statins, although between 57 (high-risk HBV positive population) and 5,209 (lower-risk population) patients needed to be treated in order to prevent one case of HCC. Although some concerns were raised over safety of statins in patients with chronic liver disease, it has been shown in a randomized trial that statin-induced hepatotoxicity was lower than expected (10).

However, many questions arise: is the beneficial effect of statins HCC chemoprevention applicable to all statins? Is there a minimal dose or length of exposure to statins? Is this strategy applicable to all subgroups of patients?

In a future issue of *Hepatology*, Goh *et al.* (11) report on their unique cohort of more than 7,000 CHB patients followed in Samsung Medical Center (Seoul, Korea). Their work aimed to examine the association between statin use and the risk of incident HCC in this high-risk cohort, by adjusting on important potential risk factors. Focusing on predefined subgroups of patients and the cumulative exposure to statins (defined by the cumulative defined daily dose or cDDD), this study brings up new evidence in favor of statins HCC chemoprevention.

One of the main findings of the study lies in the low adjusted HR of 0.36 (95% CI: 0.19–0.68) associated with statin use, almost as low as that achieved with antiviral treatment (0.27, 95% CI: 0.23–0.32). The association with statin use and lower risk of HCC development applies especially for lipophilic statins [HR (95% CI), 0.35 (0.16–0.78)] such as atorvastatin, simvastatin, pitavastatin and fluvastatin, whereas marginal statistical significance was observed for hydrophilic statins. Furthermore, a clear dose-response relationship was found, based on cDDD. Finally, the association between statin use and HCC development was confirmed in predefined subgroup analyses.

The strength of this study lies in (I) the long follow-up period (median 7.2 years), (II) the large number of incident HCC cases (702 cases, 9.1% of the cohort) and (III) adjustments on potential risk factor for HCC development and especially liver cirrhosis, serum HBV DNA levels and anti-viral treatment.

Nevertheless, these findings must be tempered by some of the limitations of this study. It is a retrospective single-center study which focuses on an extremely peculiar population: the predominant HBV genotype in Korea is C, which is associated with a higher-risk of HCC when compared to other genotypes (12). As acknowledged by the authors, this study calls for external validation studies in other ethnicities and in other HBV genotypes.

Is this study sufficient to infer causality between statin use and HCC chemoprevention? Certainly not, even though it adds another brick in the wall of statin recommendation in patients at a high-risk for HCC. A final response should come from the numerous currently ongoing or recently terminated prospective trials.

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