Perspective

Do statins reduce the risk of hepatocellular carcinoma in patients with chronic hepatitis B?

James Fung[1,2], Ching-Lung Lai[1,2], Man-Fung Yuen[1,2], Irene Oi-Lin Ng[2,3]

[1]Department of Medicine, The University of Hong Kong, Hong Kong SAR; [2]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong SAR; [3]Department of Pathology, The University of Hong Kong, Hong Kong SAR

Corresponding to: James Fung, MD. Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong. Email: jfung@gastro.hk.

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In subjects with chronic hepatitis B (CHB), the lifetime risk of developing hepatocellular carcinoma (HCC) is estimated to be 25-37 times compared to non-infected subjects. The process of hepatocarcinogenesis is complex and involves well-documented host, viral, and environmental risk factors. The most important risks include host factors such as older age, male gender, the presence of cirrhosis, and viral factors such as the viral load, genotype, and the presence of basal core promoter mutations. To date, antiviral therapy is the only intervention demonstrated to significantly reduce the risk of HCC development in CHB patients. Although oxidative stress has been implicated in cancer development, there is no established benefit shown from treatment with antioxidizing agents such as silymarin, green tea, and vitamin E.

Recently, there has been emerging interest in the potential role of statins in the primary prevention of HCC in CHB patients. Beyond their well-established role in preventing cardio- and cerebro- vascular complications, the use of statins have also been associated with other beneficial effects including reducing the risk of cancer. However, the anti-neoplastic property of statins has not been consistently shown. In a population-based study from Denmark, there was no significant reduction in liver cancer with the use of statins, although a slightly reduced cancer incidence was observed (1). El-Serag *et al*., in a study analyzing 1,303 cases of patients taking statins with 5,212 matched controls, showed that statin use was associated with a significant reduction in HCC development among patients with diabetes (2). The adjusted odds ratio (OR) for any statin prescription was 0.74 [95% confidence interval (CI), 0.64-0.87], although the effect was attenuated in a sub-analysis of patient without known liver diseases (OR 0.63). In another population-based case-control study from Taiwan, Chiu *et al*. examined 1,166 liver cancer cases with an equal number of controls matched for age and sex (3). The adjusted OR was 0.62 (95% CI, 0.42-0.91) for the group which had been prescribed statin at <215.4 defined daily dose (DDD) and 0.63 (95% CI, 0.37-1.06) for the group with cumulative statin use ≥215.4 DDD. Although the use of statin was associated with a reduced risk of liver cancer in this study, a dose-response relationship was not observed. The authors surmised that the numbers might have been too small to demonstrate a significant difference with various doses.

In a recent study published in the Journal of Clinical Oncology, Tsan *et al*. described a population-based cohort study from Taiwan of CHB patients, demonstrating that statin use may reduce the risk of HCC in patients infected with HBV in a dose-dependent manner (4). A total of 33,413 CHB patients from the Taiwanese National Health Insurance research database were included in the cohort, of which 8.3% had used statins. There were 1,021 cases of HCC during the follow-up period, with an overall incidence rate of 310.4 cases per 100,000 person-years. The incidence rates of HCCs were 319.5, 260.5, 198.1, and 158.7 and the adjusted OR were 0.66 (95% CI, 0.44-0.99), 0.41 (95% CI, 0.27-0.61) and 0.34 (95% CI, 0.18-0.67) for patients with statin use of 28 to 90, 91 to 265, and over 365 cumulative DDD respectively.

However, even after controlling for potential confounders, using results extracted from a database not designed for this specific purpose has limitations. Powerful

predictors such as the presence of cirrhosis and the use of antiviral therapy were accounted for, but only within the limitations of their database. It is very likely that those with bridging fibrosis and early cirrhosis will not be identified in such a database, as the majority will be asymptomatic. Previous studies have shown the beneficial effect of antiviral therapy in reducing HCC risk in CHB (5,6), and profound and durable suppression of hepatitis B virus is likely to have greater effect in preventing HCC compared to statins. However, antiviral therapy is also reduced to a binary variable, without further analysis on the duration and efficacy of therapy. The duration of therapy and the virological response to antiviral therapy are likely to be more important factors than simple exposure to antiviral treatment. Important viral factors such as genotype, the presence of core promoter mutations, HBeAg status, and the level of HBV DNA also are not accounted for. Unfortunately these variables are unlikely to be available from such a database, and the authors appropriately adjusted for potential available cofounders such as age, sex, cirrhosis, diabetes, antiviral therapy, angiotensin converting enzyme inhibitors, and aspirin.

It is important to note that the authors allowed 2 years of follow-up to ensure adequate exposure before analysis of data. Theoretically, all HCC diagnosed within these 2 years should have been excluded. In the survival curve shown, this appears to be the case for the cohort stratified to those taking statin 28-90, 91-365, and >365 cumulative DDD. For those with a cumulative DDD <28, the incidence of HCC was also shown within the initial 2 years. One assumes that in the actual analysis, the lead-in of 2 years applied to all groups, that is, any HCC occurring within the first 2 years in the group with a cumulative DDD <28 were also discounted. If this was not performed, the question arises whether a significant difference will remain (as the incidence curve will shift towards the right), rendering the analysis invalid.

Despite the limitations mentioned above, Tsan *et al*. have demonstrated the potential benefit of statin in HCC reduction in CHB patients. The mechanisms by which statins can prevent HCC remain largely speculative. Possible mechanisms include interference of the mevalonate pathway, leading to reduction of its downstream products important in activation of various cellular proteins responsible for promoting apoptosis (7). Apart from inducing apoptosis, statins have also been shown to impair cell cycle progression, reduce cellular adhesion, modulate angiogenesis, and promoting growth inhibition (8-12). Particular to HBV, statins, through the inhibition of cholesterol synthesis and augmentation of oral antiviral therapy, may reduce HBV replication (13).

The evidence thus far provided by 3 large population studies demonstrates the potential chemo-protective effect of statins against HCC, and merits further attention. Whether statins can genuinely reduce the risk of HCC in CHB patients can only be answered by well-designed randomized controlled trials with sufficient power. If statins are definitively shown to reduce HCC in CHB patients, the paradigm may be reversed from statins being potentially hepatotoxic to their having beneficial effects for those with liver diseases.

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