PROF. LUCA G. G GUIDOTTI (Orcid ID : 0000-0002-0205-2678)

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Low-dose aspirin reduces the risk of HBV-associated HCC even when administered short-term: too good to be true?

Luca G. Guidotti[1,2], Carlo La Vecchia[3], Massimo Colombo[4]

[1]Division of Immunology, Transplantation and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy.

[2]Vita-Salute San Raffaele University, Milan, Italy.

[3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[4]Liver Center & General Medicine, IRCCS San Raffaele Hospital, Milan, Italy

Correspondence: Prof. Massimo Colombo
Liver Center & General Medicine, IRCCS San Raffaele Hospital, Milan.
Telephone: +39 335 5719512
Email: mcolombo46@yahoo.it, colombo.massimo@hsr.it

Mass vaccination campaigns against hepatitis B virus (HBV) and treatment of chronic HBV carriers with oral nucleos(t)ide analogues (NUCs) represent the pillars of World Health Organization (WHO) campaigns aiming to curb life-threatening complications of chronic hepatitis B (CHB), including hepatocellular carcinoma (HCC) [1]. Over 250 million people worldwide remain persistently infected with HBV and less than 3% of them are currently covered by NUC treatment [2]. This notion, coupled with the evidence that even lifelong NUC regimens may not eliminate the risk of HCC [2], prompted to assess additional strategies for cancer prevention.

Particular attention in recent years has been given to largely prescribed, over-the-counter (OTC) drugs that may possess anti-HCC potential. In this context, aspirin at low doses - owning platelet-specific effects with minimal anti-inflammatory or analgesic/antipyretic properties [3] and long assumed to reduce the risk of developing different solid tumors in humans [4,5] - has been shown to prevent and/or delay the onset of HCC in animal models of chronic HBV infection [6,7]. Mechanistically, the sustained inhibition of platelet function by low-dose aspirin reduces the intrahepatic accumulation of pathogenic HBV-specific $CD8^+$ T cells that would otherwise trigger immunopathological responses leading to fibrosis, cirrhosis and HCC [6,7].

These preclinical studies have been supported by epidemiological evidence that evaluated the risk of HCC in patients suffering from liver diseases, particularly chronic HBV and HBV infections. Indeed, most of these studies reported that a regular and long-term use of low-dose aspirin is associated with reduced HCC incidence and mortality, with little or no excess risk of gastrointestinal bleeding [8-18].

Along these lines, in a recent article proposed by Hepatology, Jang et al. conducted a record-linkage cohort study of low-dose aspirin and HCC among more than 300,000 Korean CHB patients over a ten-year period (2007-2017) [19]. By defining patients treated with aspirin as those individuals receiving aspirin prescriptions for 90 or more consecutive days, the authors derived a propensity score-matched cohort of 19,003 pairs [19]. With a median follow-up of 6.7 years, 2697 patients developed HCC, 1232 in the treated and 1465 in the untreated group [19]. The 10-year cumulative incidence of HCC

was 9.5% in the treated vs 11.3% in the untreated group, corresponding to an adjusted hazard ratio (HR) of 0.85 (95% confidence interval, CI, 0.78-0.92) [19]. Aspirin use for 90 or more consecutive days was therefore inversely related to HCC, but there was no evidence of a duration-risk relationship: when the analysis was restricted to the 14,689 CHB patients who had used aspirin for more than 1 year (and 14,689 untreated), the HR was 0.86 (95% CI 0.78-0.94) [19].

A stratified analysis was also provided for non-cirrhotic versus cirrhotic patients treated or not with aspirin. Among the non-cirrhotic patients, 900 cases of HCC were registered in individuals who received aspirin treatment, while there were 1059 HCC cases in untreated individuals, corresponding to an HR of 0.87 (95% CI 0.79-0.95) [19]. By contrast, there was no association with aspirin use and reduced HCC risk among cirrhotic patients: 323 and 333 HCCs were observed in aspirin-treated versus aspirin-untreated cirrhotic individuals, corresponding to an adjusted HR of 1.00 (95% CI 0.85-1.15) [19]. The latter finding may depend on the cirrhosis-linked thrombocytopenia, which could have weakened the capacity of aspirin to inhibit platelet function [19]. However, the divergency of results between non-cirrhotic and cirrhotic patients was of borderline significance (p for interaction, 0.04) and was less evident in a sensitivity analysis using a 1:3 (instead of a 1:1) propensity score-matched cohort, where the HR was 0.81 among non-cirrhotic and 0.94 among cirrhotic patients [19]. Likewise, when liver disease-related mortality was considered, the overall HR was 0.80 (95% CI 0.71-0.90); the HR was lower among non-cirrhotic individuals (0.84) versus cirrhotic ones (0.91), but the heterogeneity was not significant. Hence, it is plausible that a favorable effect of aspirin on HCC may be greater in patients without cirrhosis, but a similar effect cannot be excluded in patients with cirrhosis. A multivariate analysis on all cohorts - in addition to the propensity score-derived datasets - could provide more precise quantifications. Major bleeding was reported in 1783 patients (908 treated with aspirin, 830 untreated), corresponding to an overall adjusted HR of 1.09 (95% CI 0.99-1.07). The HR was apparently greater in cirrhotic patients (1.15) than in non-cirrhotic ones (HR 1.05) but, again, the heterogeneity was not significant [19].

The findings of this Korean report are consistent with those of two studies from Taiwan and Sweden, both of which used a similar record-linkage design [14,18]. The inverse association between aspirin use and HCC risk, however, appears less strong in the Korean study. The multivariate HRs of HCC for aspirin-treated versus aspirin-untreated patients were 0.68 in the Taiwanese study of CHB patients [14] and 0.69 in the Swedish study, which included patients chronically infected with HBV or HCV and used a standard full cohort analysis rather than a propensity score design [18]. At variance with the Korean report, the Swedish study also documented a strong inverse duration-risk relationship, with an HR of 0.57 for the use of aspirin at 5 years or more as compared to its short-term use (3 months to 1 year) [18].

All these studies share similar strengths, i.e., cohort designs with defined measures of exposure and outcome, large sample sizes and allowance for a considerable number of covariates. Aspirin is a widely available and cheap drug and exposure information based on prescription record-linkage does not necessarily include OTC sales. The possible bias introduced by OTC sales is, however, probably unrelated to HCC outcome, and – if anything – should lead to an underestimate of the association. In keeping with this, findings from five cohort and case-control studies that were pooled in a meta-analysis and that were based on aspirin exposure (where the information about exposure was collected at direct interview and, therefore, was not affected by the bias above-mentioned) revealed that the overall pooled relative risk was 0.71 for HCC and 0.62 (95% CI 0.44-0.86) for all hepato-biliary cancers [15].

The implications from this Korean report must be taken with caution due to the limited strength of the association between aspirin use and HCC risk and the rather surprising absence of duration-risk relationship. This is particularly difficult to interpret for a disease like CHB-associated HCC, which normally develops after several decades of persistent, immune-mediated liver injury [20]. However, the overall evidence now available from three record linkage reports [14,18,19] and five additional studies [15] allows to confidently conclude that the regular use of low-dose aspirin has a favorable effect on HCC risk in CHB patients.

Since this Korean study reported a moderate excess in the risk of bleeding as documented in the previous Taiwanese and Swedish studies [14,18] (in the order of 10%, not significant in each single study but similar across various populations) it remains to be debated whether it is now time to recommend aspirin treatment initiation in selected patient populations or whether it is better to await for improved biomarkers predicting HCC risk and/or dedicated and randomized clinical trials. To the least, this additional study by Jang et al. [19] should encourage a discussion as per the future of anti-platelet therapies in CHB patients.

Conflict of Interest

L.G.G is a member of the board of directors and stockholder at Genenta Science, member of the Scientific Advisory Board at Antios Therapeutics and Ananda Immunotherapies and participates in advisory boards/consultancies at Gilead Sciences, Roche, Arbutus Biopharma and Chroma Medicine.

M.C. participates in advisory boards for Galapagos,Exelixis and Target HCC.

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