JOURNAL
OF HEPATOLOGY

Reply to: "Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: Relevance of non-characterized nodules – A response"

To the Editor:

We appreciate the interest generated by our manuscript,[1] and thank Dr. Pol *et al.* for their letter,[2] and the Editor for giving us the opportunity to respond.

We first want to address and clarify the issue raised regarding the lack of an untreated internal control group in our study. Actually, it is not feasible to find an optimal contemporaneous untreated cohort. It also seems unethical to run a randomized trial *vs.* no treatment. Hence, no head to head comparison is currently realistic in our environment. Thus, in our setting the only possible control group for the new treatments arm (direct-acting antiviral [DAA]-treated patients) is a prior cohort of patients on interferon regimens. Accordingly, we made the comparisons based on those patients from our cohort who met the inclusion's criteria from the HALT-C[3] and Epic[4] cohorts, and who would have been treated with interferon-based regimens.

While we could agree that baseline comparability is essentially difficult in observational studies, this is the only current achievable design due to outstanding ethical and logistic arguments against conducting a randomized clinical trial. In this scenario, any observational study, even the two studies referred to by Pol *et al.*,[5,6] also had to rely on statistical tools to handle confounders and population differences, since randomization was not feasible. In our case, sensitivity analyses were conducted by means of a restricted selection of patients with similar characteristics from cohorts HALT-C[3] and Epic[4] for the comparison of DAA versus interferon-based regimens. We also did an analysis including the patients with the highest risk of hepatocellular carcinoma (HCC) according to current knowledge.[7]

Pol *et al.* state that the results presented in this paper are in contrast to those of a recent report by Toyoda *et al.*[5] Actually, that manuscript concluded that they did not find any difference, rather than suggesting a protective effect of DAA therapy. Please note that a non-significant *p* value does not validate the null hypothesis ("Absence of evidence is not evidence of absence"[8]), as seems to be suggested in the letter by Pol *et al.*[2] Thus, our data are not contradictory to those results.

In addition, we should also note that patients from Toyoda *et al.*[5] were a very low risk population (only 30% cirrhosis, all compensated), thus reducing the possibility of events even more; indeed, 70% of them were at such negligible risk that they may not have undergone HCC screening, which is usually performed in patients with cirrhosis.

While the similarity in HCC rates reported in DAA-treated patients across cohorts is acknowledged, the argument regarding inconsistencies in the rates of HCC for DAA-treated and untreated patients is not correct. In fact, there are inconsistencies in their argumentation since, for instance, unadjusted rates of HCC were larger in the DAA-exposed group than in the untreated patients (1.40 and 0.56 per 100 person-years, respectively), as shown in the paper from Carrat *et al.*[6] Indeed, the rate of non-cirrhotic patients in Carrat *et al.*[6] was 58%, while this was almost 50% in Toyoda *et al.*[5] Again, this may suggest that these patients would not have undergone HCC screening.

In essence, it has to be noted that our aim was to estimate the risk of HCC in a cohort of cirrhotic patients treated with DAAs. Our results expose a clear-cut time association between interferon-free treatment and HCC development. Notably, the empirical cumulative probability function of developing HCC grows more quickly than that observed in interferon-based regimens. Pol *et al.* argued that the DAA-associated risk of HCC is not an issue anymore and that any discordant view is because of seriously flawed studies. We argue that different studies may lead to different results which might be due to different populations, methods, or even random variation. More importantly, not all apparent discrepancies are to be explained by bias. Ignoring discrepancies and imputing any apparent contradictory result to bias, is, in fact the maximum exponent of bias.

Conflict of interest

ZM: Speaker fees from Abbvie, Gilead, Janssen, MSD; Advisor for Gilead. XF: Unrestricted grant support from Abbvie and advisor for Abbvie and Gilead. FT: fees from ImClone, Daiichi-Sankyo Pharma Development, ArQule and Rovi. Speaker fees from Bayer. MR: Consultancy from Bayer, BMS, Roche, Ipsen, AstraZeneca and Lilly. Lecture fees from Bayer, BMS, Gilead, and Lilly. Research grants from Bayer. JB: Consultancy from Arqule, Bayer, Novartis, BMS, BTG- Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance, Roche, AbbVie, Merck, Sirtex, Ipsen, AstraMedimmune, Incyte, Quirem, Adaptimmune, Lilly. Research grants from Bayer and BTG. Educational grants from Bayer and BTG. Lecture fees from Bayer, BTG- Biocompatibles, Eisai, Terumo, Sirtex, Ipsen. JR: Consultancy for Boehringer Ingelheim, Smith & Nephew SAU, FERRER INTERNACIONAL and Novartis. Speaker fees from Boehringer Ingelheim, Novartis, Spherium Biomed, SOLTI, BCNSCIENCE, ROVI and SFJ Pharmaceuticals. VS: Travel fees from Bayer.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.04.018.

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