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

To the Editor

We read with interest the paper by Mariño *et al.* which suggests an increased risk of hepatocellular carcinoma (HCC) in cirrhotic patients treated with direct-acting antivirals (DAAs), (3.7%/100 person-years [PY]) especially in those with undetermined nodules before treatment (9.6%/100 PY).[1]

We would like to dispute the conclusions reached by the authors that there is a clear-cut time association between interferon-free treatment and an increased risk of HCC:

1. No valid conclusion regarding the effect of DAA on HCC risk can be drawn from this study as all patients included in this retrospective cohort were given DAAs. To be valid, a comparison with similarly untreated patients in the cohort is needed.
2. Comparisons with patients eligible for interferon (IFN)-based therapy from historical cohort studies are at high risk of selection bias, as criteria to initiate IFN-based treatment exclude the most severe patients (Child-Pugh B or C) who received DAAs in the present report.
3. The results presented in this paper are in contrast to recent prospective reports which did not demonstrate an increased risk of DAA-related occurrence or changes of non-hypervascular hypointense nodules by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging in 401 DAA-treated patients.[2]
4. Finally, the reported rates of HCC of 2.93% HCC/100 PY (95% CI 2.20–3.90) in patients with Child-Pugh A cirrhosis are in line with those of the ANRSCO22 Hepather study:[3] the corresponding crude rate in DAA-treated patients was 2.72/100 PY (95% CI 2.32–3.17) (*i.e.* 166/6,104 PY) in 3,045 patients with Child-Pugh A cirrhosis, without any evidence of an increased rate over the first 12 months following the start of treatment; the rate was 3.70/100 PY (95% CI 2.80–4.80) (*i.e.* 57/1,539 PY) in untreated patients. Thus, if the HCC rates reported in DAA-treated patients appeared consistent across cohorts, in unadjusted as well as multivariable adjusted analyses, the HCC rate was lower in DAA-treated than the corresponding rate observed in untreated patients.

Therefore, conclusions raised in this paper appear to be seriously flawed; we, among others, no longer consider the DAA-associated risk of HCC to be an issue, even if the impact of DAA on the tumor growth and aggressiveness remains to be prospectively evaluated.

Conflict of interest

Pr. Pol reports grants and personal fees from Gilead, grants and personal fees from BMS, grants and personal fees from MSD, grants and personal fees from Abbvie, personal fees from Janssen. Dr. Fontaine reports personal fees from Gilead, Abbvie, BMS, MSD, Janssen. Pr. Carrat has nothing to disclose.

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.2019.02.025.

References

[1] Mariño Z, Darnell A, Lens S, Sapena V, Díaz A, Belmonte E, et al. Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: relevance of non-characterized nodules. J Hepatol 2019;70:874–884. https://doi.org/10.1016/j.jhep.2019.01.005.

[2] Hidenori T, Takashi K, Toshifumi T, Kazayuki M, Yasuhiro S, Tomoyuki A, et al. The impact of HCV eradication by direct-acting antivirals on the transition of precancerous hepatic nodules to HCC: a prospective observational study. Liver Intern 2019 (in press).

[3] Carrat F, Fontaine F, Dorival C, Simony M, Diallo A, Hezode C, et al. ANRS CO22 Hepather cohort. Clinical outcomes in patients with chronic hepatitis C following direct-acting antiviral therapy: a prospective cohort study. Lancet 2019, pii: S0140-6736(18)32111-1. doi: 10.1016/S0140-6736(18)32111-1.

Stanislas Pol[1,2,*]
Hélène Fontaine[1]
Fabrice Carrat[3,4], on the behalf of the ANRS/AFEF Hepather Study group

[1]*Assistance Publique – Hôpitaux de Paris, Hôpital Cochin, Département d'Hépatologie, Paris, France*
[2]*Université Paris Descartes, INSERM U-1223 et USM20, Institut Pasteur, Paris, France*
[3]*Sorbonne Université, Institut National de la santé et de la Recherche Médicale, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France*
[4]*Assistance Publique – Hôpitaux de Paris, Hôpital Saint-Antoine, Unité de Santé Publique, Paris, France*

*Corresponding authors. Address: Département d'Hépatologie, Hôpital Cochin, 27 rue du faubourg Saint Jacques, 75679 Paris Cedex 14, France. Tel.: +33 1 58 41 30 01; fax: +33 1 58 41 30 15.
E-mail address: stanislas.pol@aphp.fr