Journal for ImmunoTherapy of Cancer

Response to a letter to the editor: a better understanding of Immune Checkpoint Inhibitor-induced cholangitis for better management

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To cite: Coukos A, Vionnet J, Sempoux C, *et al*. Response to a letter to the editor: a better understanding of Immune Checkpoint Inhibitor-induced cholangitis for better management. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e006877. doi:10.1136/jitc-2023-006877

Accepted 16 February 2023

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We have the pleasure to further the conversation around checkpoint inhibitor-induced liver injuries or, as Hountondji *et al* have elegantly coined them, CHILI.[1] We would first like to thank Meunier and Maria for their interesting letter in response to our publication.[2]

They refer, namely, to their submitted series by Hountondji *et al*, in which 117 patients were studied, with a liver biopsy performed in 40%.[1] This large cohort will be an important addition to the scientific literature regarding this subject.

A key difference between our two studies is that we defined a toxicity's phenotype (hepatitic, cholangitic, or mixed) based on histology, whereas Hountondji *et al* defined it based on laboratory values, an interesting approach since not all patients in standard care are subject to a liver biopsy. They used the R ratio, which categorizes liver injury by the ratio of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) {(ALT/ULN)/(ALP/ULN)}, ignoring aspartate aminotransferase, gamma-GT and bilirubin. This defines injuries as hepatocellular (R>5), mixed (R 2–5) or cholestatic (R<2).[3] In our study, similarly to the publication by Cohen *et al*, we found a correlation between the global liver function test (LFT) profile and the histological phenotype.[4] In 21 of 25 patients (84%), the histological and the global LFT phenotypes were the same, whereas when using the R ratio, this was the case in only 13 of 25 patients (52%). This further strengthens the argument for performing liver biopsies in CHILI as well as the need for a more specific clinical score.

An important point highlighted in the letter is the increasing evidence that cholangitic forms of checkpoint inhibitor-induced liver injury (IrC) more frequently exhibit resistance to corticosteroid therapy than hepatocellular forms, thus often requiring second-line immunosuppression. In their experience, the frequency of IrC may be higher than previously described, highlighting the pertinence of in-depth studies regarding this subject. They cite the paper from Pi *et al*, which describes numerous patients with IrC and finds an increased frequency of corticosteroid-resistance in IrC cases.[5] Moreover, they show the potential for ursodeoxycholic acid (UDCA) use in this syndrome, a topic not explored in our study. Their results seem promising, opening the door for additional corticosteroid-sparing agents. We agree that further prospective studies on the use of UDCA in this context would prove beneficial. Meunier and Maria also mention the relatively low number of cholangitic control patients in our study. As we stated in the text, this situation is related to the fact that liver biopsy is not compulsory for the diagnosis of primary biliary cholangitis (PBC) and rarely performed in clinical practice.

Another element underlined in this letter was the lack of checkpoint inhibitor-induced primary sclerosing cholangitis (PSC)-like injuries in our study. These forms were actually not excluded at the onset, but we did not identify any after thorough evaluation, including MRI of the liver. Importantly, cholangio-MRI examinations were available in all cholangitic and mixed forms of liver injury and were systematically found to be normal. The retrospective nature of our study and the fact that liver biopsies are often reserved for severe or uncertain cases makes identifying these types more difficult. We excluded PSC–PBC overlap syndromes in the control group to avoid an overcomplicated and non-uniform control group. We fully agree that specifically

including these cases, notably using a prospective design, would provide valuable insight into their management.

Ultimately, we agree with Meunier and Maria on the importance of liver biopsies in the diagnosis of CHILI and agree that a specific scoring system for hepatic injury in these cases may aid in increasing the correlation between pathology and biology. The latest guidelines from the European Society for Medical Oncology propose to consider a liver biopsy for grade 3 and 4 toxicities, in contrast with previous recommendations to do so only for grade four toxicities.[6] Continuing to perform liver biopsies in CHILI patients will be key to decipher and understand these entities. Prospective studies including a morphological substrate are now needed to develop specific scores to guide oncologists, hepatologists and immunologists in the management of CHILI.

Contributors All authors contributed and approved the final paper. CS and MF share last authorship.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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