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Better understanding of ICI-induced cholangitis for better management

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We read with interest the recent report about histology in liver injury induced by immune checkpoint inhibitors (ICIs) published by Coukos *et al*.[1]

In this study, the authors compared the histological lesions of ICI-induced hepatitis (n=27) with those of autoimmune hepatitis (n=11) or primary biliary cholangitis (n=3).

They observed three distinct ICI-induced histological liver injury patterns: hepatitic (52%), cholangitic (19%), and mixed (29%).[1]

In our own experience based on a multicenter series of 117 patients with ICI-induced hepatitis with about 40% of patients who underwent liver biopsy, we report a different distribution of clinical patterns with more cholestatic forms (hepatocellular: 38.5%, cholestatic: 36.8%, and mixed: 24.8%).[2]

As for other drug-induced liver injury (DILI), we used the ratio R ((ALT/ULN)/(ALP/ULN))[i] for the characterization of the clinical pattern of the ICI-induced hepatitis.[2] In our experience and that reported by Cohen *et al*, there is a significant correlation between the biochemical profile and liver histology.[3]

Coukos *et al* defined the pattern of liver injury on the basis of histological analysis. In practice, it would be interesting to correlate histological lesions with biological patterns.

Recently, Pi *et al* had specifically studied immune-mediated cholangitis from published case report.[4] A total of 53 cases of ICI-induced cholangitis were included in this review: 12 with small-ducts type, 29 with large-ducts type, and 12 with mixed type. Various biliary injuries have been described but the biological profile of these cholangitis is that of cholestatic hepatitis (R<2).

In their study, Coukos *et al* excluded primary sclerosing cholangitis. From the authors' point of view, the patients included had no biliary tract abnormalities, but it is not specified whether all patients had a cholangio-MRI evaluation.[1]

To complete these explorations and improve the understanding of ICI-induced hepatitis, it would be interesting to compare the histological abnormalities of these secondary sclerosing cholangitis with those of primary sclerosing cholangitis.

Also, in the review by Pi *et al*, among the 53 patients with ICI-induced cholangitis, 16 (30%) patients required second-line immunosuppressive therapy.[4] Corticosteroids seems to be less effective for the treatment of ICI-induced cholangitis, in contrast to hepatocellular clinical pattern. Indeed, only 8.5% of patients had a complete biochemical response to immunosuppressive therapy. It is interesting to note that 20 patients received ursodeoxycholic acid (UDCA) associated with corticosteroids.

Interestingly, in the study by Coukos *et al*, the authors reported a high failure rate to corticosteroids (56%) and the need for second-line treatments for 14 patients.[1] These rates are higher than those usually reported in the literature for all pattern of ICI-induced hepatitis. Cholestatic pattern seem to be more resistant to corticoids in this study (75%), which is consistent with other data in the literature. But there are no data regarding the use of UDCA in these patients.

UDCA is well tolerated and safe and is the first-line reference treatment for primary biliary cholangitis and primary sclerosing cholangitis. In our experience, some patients with cholestatic hepatitis improved with AUDC alone without corticosteroids. However, the position of ursodeoxycholic acid (UDCA) in the guidelines is not well defined, but its interest is mentioned.

Future studies should be conducted to confirm the benefit of AUDC alone or in combination with corticosteroids, especially in ICI-induced cholangitis.

Finally, regarding the assessment of hepatitis severity, the authors use the following

[i]ALT: Alanine transferase; ULN: Upper the limit of normal; ALP: Alcaline phosphatase.

classification in their study: mild (ALT <400 U/L and total bilirubin <40 µmol/L), moderate (ALT >400 U/L and <1000 U/L and total bilirubin <40 µmol/L) or severe (ALT >1000 U/L and/or total bilirubin >40 µmol/L). Usually, adverse events of anticancer treatments are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) classification, but this classification does not reflect hepatic severity.[5] For other DILI, it is recommended to use the DILIN score to assess the severity of hepatitis. In the study, the biological classification used did not correlate with histological severity. These results further support the need to use a more specific liver function score to assess the severity of ICI-induced hepatitis.

Overall, this work is very interesting and the comparison of ICI-induced hepatitis with autoimmune hepatitis or primary biliary cholangitis improves the understanding of these adverse effects. However, the exclusion of macroscopic cholangitis and the small number of primary biliary cholangitis limits the analysis of this type of ICI-induced hepatitis. The high rate of corticosteroid resistance in this study could be explained by ICI-induced forms of cholangitis. In these patients, the potential value of AUDC, while discussed in the guidelines, may be be useful in clinical practice as reported in some case reports or our own series.[2 4] The study by Coukos *et al* eventually raises the need for a better correlation between biology and histology to assess the severity of ICI-induced hepatitis and better define therapeutic management of this frequent immune-related adverse event.

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