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Editorials

Emerging role of immunotherapy for cancer as a major cause of drug-induced liver injury

The epidemiology of drug-induced liver injury (DILI) is changing as researchers identify new triggers of liver damage, including COVID-19 vaccines, turmeric, green tea extract, and immunotherapy drugs. A thorough literature review by Fontana *et al.* [1] found that the causes of DILI have shifted in the United States. Previously recognized hepatotoxic drugs, such as phenytoin and carbamazepine, are now less frequently reported. This decrease may be related to the use of safer anti-epileptic drugs. In contrast, biological agents that impact the host immune system, such as infliximab and immune checkpoint inhibitors (ICIs), are, nowadays, the main cause of DILI [2,3]. More than 230 anticancer drugs were approved in the U.S. between 1950 and 2022, and these compounds are a clear and current example of the growing incidence of DILI. According to the LiverTox database, 47 % of antineoplastic agents have been implicated in causing clinically apparent liver injury [4].

Antineoplastic drugs are classified into three groups: - traditional cytotoxic drugs (e.g., cyclophosphamide, doxorubicin, methotrexate, mercaptopurine, oxaliplatin, asparaginase, temozolomide), - hormonal therapies (e.g., tamoxifen, letrozole, exemestane, bicalutamide, abiraterone, cyproterone) and - targeted drugs (e.g., monoclonal antibodies, tyrosine kinase inhibitors, and small molecule inhibitors). The best-documented hepatotoxicity in this last category is associated with ipilimumab, nivolumab, pembrolizumab, imatinib, palbociclib, pazopanib, bortezomib, pembrolizumab, imatinib, pazopanib, and bortezomib [4].

Monoclonal antibodies have been shown to be effective in treating various types of cancer, including solid tumors, hematological neoplasia, renal cell carcinoma, Hodgkin lymphoma, lung cancer, hepatocellular carcinoma, and melanoma [5,6]. ICIs target specific immune checkpoint proteins, such as programmed cell death protein 1 (PD-1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), blocking the inhibitory signals that prevent immune cells from attacking cancer cells [5,6]. In ICI-induced DILI, nearly all organs are targeted by a broad spectrum of immune-related adverse events. However, the skin, digestive tract, lungs, endocrine glands, neurological system, kidney, blood cells, liver, and musculoskeletal system are the most commonly affected. Given that these drugs are often recommended for the treatment of several types of malignancies nowadays, ICIs have been a well-recognized cause of DILI in clinical practice, and it is predicted to become increasingly common over time [5]. Depending on whether these drugs were administered as combination therapy or as monotherapy, the incidence of hepatotoxicity has varied from 2 % to 25 % [3]. Liver biopsy can be a useful auxiliary tool to detect specific patterns of hepatobiliary damage (granulomas, endothelitis, and sclerosing cholangitis) [7].

In a study conducted by Zheng *et al.* [8], the hepatotoxicity profile, DILI spectrum, and safety ranking of ICIs for cancer treatment were evaluated through a systematic review and network meta-analysis, reinforcing the presumption of ICI-induced DILI enhancement. The analysis included data from 106 clinical trials involving approximately 65,000 patients who were randomized to 17 different treatment regimens. They found that the overall incidence of hepatotoxicity was ~4 %, and the rate of fatal liver adverse events was 0.07 %. In terms of combined therapies, patients receiving treatment with a PD-1 inhibitor, targeted therapy drug and chemotherapy experienced the highest risk of a significant increase in aminotransferases levels across all grades. When it comes to immune-related hepatotoxicity, there was no significant difference in the risk of liver damage between PD-1 and CTLA-4 inhibitors across all grades. However, CTLA-4 inhibitors were found to be associated with a higher risk of grade 3-5 liver toxicity compared to PD-1 inhibitors. These findings suggest that treatment with ICI carries a higher risk of liver damage than chemotherapy in cancer patients. Moreover, combination therapy with ICIs showed an increased risk of drug-induced liver injury compared to ICI monotherapy.

In a retrospective cohort study, Atallah *et al.* [9] monitored 432 patients who had received ICIs over the course of ten years. Based on established case definitions, they found a DILI incidence of 11.5 out of 1000 persons-months. The researchers also described that in 19 % of cases where liver toxicity was suspected, an alternative cause was identified by the clinicians after formal evaluation. This highlights the importance of systematic evaluation by clinicians to avoid unnecessary immunosuppression. The same authors found that patients on combination therapy for 4.5 months have a lower risk of developing new episodes of DILI, and therefore, the frequency of monitoring can be reduced. They also suggest that the grading system for adverse events (CTCAE) may overestimate the severity of DILI and lead to unnecessary hospitalizations and corticosteroid treatment.

The patients who experienced liver toxicity due to ICIs were found to be younger and more likely to have received combination therapy ($p < 0.001$). They also had significantly higher baseline ALT ($p = 0.003$), lower ALP ($p = 0.01$), lower neutrophils ($p = 0.03$), and lower neutrophil-to-lymphocyte ratio (NLR) ($p = 0.008$). However, there were no significant differences in terms of cancer type, BMI, presence of liver metastases, baseline lymphocytes, or eosinophils between the groups. Based on this, the authors concluded that the risk of ICI-induced liver toxicity in real-world scenarios is higher than what was previously reported [9].

Pocurull *et al.* [10] conducted a prospective study in a tertiary hospital in Spain to analyze the pattern of DILI. They recorded all referred cases with suspicion of liver toxicity from 2018 to 2023. Out of the total 106 patients who fulfilled the diagnostic criteria for idiosyncratic hepatotoxicity, 76 cases induced by paracetamol were

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excluded. The majority of cases (72 %) showed a hepatocellular pattern of liver injury. Antineoplastic agents were the leading cause of liver damage (26 %), followed by antibiotics (24 %), analgesics (12 %), and recreational drugs (9 %). Regarding individual drugs, those more commonly implicated were amoxicillin-clavulanate (12 %), nivolumab (7 %), isoniazid (7 %), atorvastatin (5 %), and metamizole (5 %). After analyzing the clinical results, it was found that 51 % of patients required hospitalization, out of which 9 % had a fatal outcome such as liver transplantation or death. It is worth noting that an additional 126 patients with drug-induced liver injury caused by immune checkpoint inhibitors were identified, but they were not referred to a hepatologist. They analyzed all ALT > 5 ULN cases during ICI therapy within the same period (2018–2023) and found 138 patients meeting the criteria for the DILI definition. Thirty-seven cases were induced by nivolumab (25 %), 35 by bevacizumab (25 %), 25 by pembrolizumab (18 %), 22 by ipilimumab (16 %), and 19 by atezolizumab (14 %). The authors stated that if these patients had been referred to the liver unit, it would represent more than 90 % of DILI cases.

This study has two main strengths. Firstly, it is an observational and prospective design where the same physicians followed all patients. Secondly, the causality assessment of DILI was made based on the RUCAM score and validated by different specialists. However, one significant drawback is that the authors only looked for ALT elevations, which could have introduced bias as other types of liver injury, such as cholestatic or mixed forms, might have gone undetected. Nevertheless, these valuable data raise an alarm, showing that cancer therapy was the most common cause of liver toxicity in a tertiary hospital.

Contrary to previous studies that showed ICIs to be the most frequent cause of DILI among these drugs, the analysis of 71 well-vetted DILI cases enrolled in the Spanish DILI Registry and the LATINDILI Network revealed that protein kinase inhibitors represented 14 % of cases, while ICIs caused only 6 % of them [11]. The majority of patients with DILI related to ICIs experienced hepatocellular damage (79 %), while 12 % had cholestatic injury. Almost 70 % of patients developed jaundice, and 49 % were hospitalized. Most of the patients had moderate injury (46 %), and 15 % suffered from severe liver damage. There were five liver-related deaths in total, four of which were from Spain and one from Latin America. The study also found that there were no chronic DILI cases, and 71 % of patients resolved spontaneously [11]. The analysis identified imatinib, asparaginase, combined schema ipilimumab/nivolumab, and methotrexate as the most common causative agents. While hepatotoxicity registries help to assess DILI frequency prospectively, liver toxicity is often underreported.

While antibiotics and painkillers have historically been the main drugs causing liver damage, it's important to note that the incidence of liver damage caused by immunotherapy drugs is not yet fully understood [12–14]. In Western countries, amoxicillin-clavulanate is the most commonly associated drug, with an estimated frequency of 1 in 2500 users [1]. In Iceland, however, the prevalence of drug-induced liver damage was higher in users of azathioprine (1 in 133) and infliximab (1 in 148), though the number of patients exposed was much smaller [15].

In conclusion, recent results suggest that anticancer immunotherapy has become a significant cause of DILI. However, well-designed prospective studies are needed to determine the frequency of this condition and how to manage it effectively. It is essential to promote collaboration between hepatologists, clinicians, and oncologists in hospitals to ensure that patients with potential liver damage are assessed together. The need for corticosteroid treatment should also be examined and monitored jointly. Additionally, including these cases in centralized databases can help gain a better understanding of the clinical management and mechanisms of this condition.

Declaration of interests

None.

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