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Letter to the Editor

Increased reporting of fatal hepatitis associated with immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICIs) have revolutionised oncology treatment for multiple cancer types, with expanding indications [1,2]. ICIs unleash anti-tumour immune responses and include antibodies targeting two main pathways critical in T-cell inhibition: cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), programmed cell death 1 (PD-1) and programmed death ligand 1 (PDL-1) [1,2]. This immune activation may also lead to immune-related adverse events (irAEs) affecting potentially any organ [1]. Hepatotoxicity—specifically immune-mediated hepatitis—has been reported in case reports and case series as well as from meta-analyses of clinical trials involving ICIs. Hepatitis is more often of low-grade toxicity, but fulminant hepatitis and death can also occur [3,4]. Incidence and prevalence as well as the risk factors of immune-mediated hepatitis and in particular of fatal hepatitis have not been defined in a large cohort.

VigiBase, http://www.vigiacces.org [5], the World Health Organization database of individual safety case reports, has already been used to describe irAEs [6–9]. We also used VigiBase to further characterise ICI-related hepatitis and moreover ICI-related fatal hepatitis. We searched the following preferred terms: 'autoimmune hepatitis', 'immune mediated hepatitis', 'hepatitis fulminant' and 'drug-induced liver injury DILI' associated with ICIs (anti–CTLA-4: ipilimumab and tremelimumab; anti–PD-1: nivolumab and pembrolizumab; anti–PDL-1: atezolizumab, avelumab and durvalumab).

By 5th September 2018, we identified 531 cases of immune-related hepatitis reported in VigiBase. We observed a substantial increase in reporting incidence over time (0.9 cases/month up to 19.25 cases/month from 2015 to 2018).

Patients had a wide spectrum of age (median: 62 [53–71.3] years), cancer types and geographical location (Table 1). Eighty-five percent (452/531) of patients were reported to have received only ICIs as suspected drugs. A total of 293 (55%) patients received anti–PD-1/anti–PDL-1 monotherapy, 91 (17%) received anti–CTLA-4 monotherapy, and 147 (28%) received combination treatment. A total of 13 patients had previously been treated with ICIs.

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The median number of doses before the onset of hepatitis was 2 [1–4], and the median onset time was 46 [26–79] days. We did not observe significant difference between monotherapy and combination therapy for time to onset of hepatitis (p = 0.47), but hepatitis occurred significantly earlier with anti–CTLA-4 (median: 34 [25–46.5] days) than with anti–PD-1/PDL-1 (median: 48 [27–118] days) (p = 0.04). Concurrent irAEs occurred in 31% (165/531) of cases, most commonly thyroiditis (n = 43) and cutaneous manifestations (e.g. dermatitis; n = 37).

Death occurred in 19% (94/490) of cases with available follow-up. We observed an increase in the number of cases of fatal hepatitis reported over the analysed period (Table 2). The median interval time between ICI initiation and the onset of hepatitis with a fatal outcome was 41 (20–146) days. Only older age (≥65 years) was significantly associated with increased mortality for patients with ICI-related hepatitis (p = 0.0094). While hepatitis was the main identifiable cause of death in 58 of 94 (62%) fatal cases, other concurrent irAEs also contributed to death in the other cases (Table 2). Fatality rates were not different with anti–PD-1/PDL-1 vs. anti–CTLA-4 monotherapy (55/293, 19% vs. 15/91, 17%; p = 0.74, respectively) or between monotherapy vs. combination therapy (70/384, 18% vs. 24/147, 16%; p = 0.70, respectively). In univariate analysis, we tested the impact, between fatal hepatitis and no fatal hepatitis, of time to onset, co-reported irAEs associated (1 or more vs no irAEs) or co-reported suspected medication (1 or more vs no other medication suspected) on the hepatitis outcome, but none of them was significantly different (p = 0.84, p = 0.065, p = 0.18 respectively).

Increase in reporting incidence of immune-mediated hepatitis reflects both increased use of ICIs, as well as heightened recognition of ICI-associated hepatitis [1]. In clinical trials, rates of grade III–V hepatitis are 0.5–6% with anti–PD-1/PDL-1 monotherapy, 1–10% with anti–CTLA-4 monotherapy and 10–17% with combination therapy [10,11]. Our cohort confirms earlier time to onset for hepatitis induced by anti–CTLA-4 than by anti–PD-1/PDL-1 [12] with 46 days of median onset time concurring with the previously reported median onset of 6–14 weeks [3,13–16]. High-grade hepatitis is more frequently described for melanoma than lung cancer [10], and time to onset could be different depending on cancer localisation and ICIs [17].

Fatal hepatitis was reported in 19% of our patient's cohort with immune-related hepatitis, which is not negligible. The only independent risk factor for fatal hepatitis was age ≥65 years. Combination ICI therapy seems to increase hepatitis incidence and severity [11], but in our cohort, we did not prove a heightened risk of fatal hepatitis with ICI combination therapy.

Our study has some limitations; no clinical data (co-reported liver disease or hepatic metastasis before ICI initiation, hepatitis grade) and no detailed differential

Table 1
Description of patients with immune checkpoint inhibitor–associated hepatitis.

Characteristics	n (%)	Data available, n (%)
Age, years; median, [IQR], (range)	62 [53–71.3] (12–93)	398/531 (75)
Male sex	306/493 (62)	493/531 (93)
Region		
Africa	2/531 (<1)	All
Americas	211/531 (40)	
Asia	55/531 (10)	
Europe	225/531 (42)	
Oceania	38/551 (7)	
Indications		
Melanoma	241/432 (56)	432/531 (81)
Lung cancer	106/432 (24)	
Renal cancer	20/432 (5)	
Other cancers[a]	65/432 (15)	
Treatment		
Monotherapy: anti–CTLA-4	91/531 (17)	All
Ipilimumab	90/91 (99)	
Tremelimumab	1/91 (1)	
Monotherapy: anti–PD-1 or anti–PDL-1	293/531 (55)	
Nivolumab	136/293 (46)	
Pembrolizumab	122/293 (42)	
Atezolizumab	28/293 (9)	
Durvalumab	5/293 (2)	
Avelumab	1/293 (<1)	
Sequential nivolumab/pembrolizumab	1/293 (<1)	
Combination	147/531 (28)	
Ipilimumab + nivolumab	139/147 (95)	
Ipilimumab + pembrolizumab	3/147 (2)	
Tremelimumab + durvalumab	5/147 (3)	
Time to onset, days; median, [IQR], (range)	46 [26–79] (1–627)	187/531 (35)
Injection number; median, [IQR], (range)	2 [1–4] (1–45)	187/531 (35)
Co-reported suspected drugs		
Patients with co-reported suspected drug	79/531 (15)	All
1 co-reported drug	37/79 (47)	
≥2 reported drugs	42/79 (53)	
Paclitaxel	10/79 (13)	
Carboplatin	7/79 (9)	
Dabrafenib	7/79 (9)	
Trametinib	6/79 (8)	
Gemcitabine	5/79 (6)	
Vemurafenib	5/79 (6)	
Others co-reported suspected drugs[b]	<5 (6)	
Fatal outcome		
All causes	94/490 (19)	490/531 (92)
Only hepatitis	58/94 (62)	
Other concurrent irAEs		
Myocarditis	4/94 (4)	
Pneumonitis	1/94 (1)	
Others causes		
Disease progression	18/94 (19)	
Infection	8/94 (9)	
Haemorrhage	2/94 (2)	
Intestinal perforation	1/94 (1)	
Toxic epidermal necrolysis	1/94 (1)	
Unknown	1/94 (1)	
Year of reporting		
2010–2015	63/531 (12)	All

(continued on next page)

Table 1 (*continued*)

Characteristics	n (%)	Data available, n (%)
2016	62/531 (11)	
2017	175/531 (33)	
2018	231/531 (44)	
Co-reported irAEs		
Patients with ≥1 irAE	165/531 (31)	All
Thyroiditis	43/165 (26)	
Cutaneous irAEs	37/165 (22)	
Colitis	33/165 (20)	
Haematotoxicity	18/165 (11)	
Hypophysitis	13/165 (8)	
Myositis	13/165 (8)	
Pneumonitis	12/165 (7)	
Myocarditis	10/165 (6)	
Adrenal insufficiency	10/165 (6)	
Myasthenia	8/165 (5)	
Nephritis	7/165 (4)	
Pancreatitis	5/165 (3)	
Others[c]	≤2/165 (1)	

CTLA-4, cytotoxic T-lymphocyte–associated antigen-4; PD-1, programmed cell death 1; PDL-1, programmed death ligand 1; IQR: interquartile range, irAE: immune-related adverse event.

[a] Cancers: head and neck (11), urothelial (8), bladder (7), hepatocellular (7), pancreatic adenocarcinoma (7), glioblastoma (3), Hodgkin lymphoma (3), multiple myeloma (3), neuroendocrine (2), prostate (2), testis (2), angiosarcoma (1), cholangiocarcinoma (1), colorectal (1), gastric (1), lymphoma (1), mesothelioma (1), ovarian cancer (1), salivary glands (1), transitional cell carcinoma (1), Vater's bulb (1).

[b] Bevacizumab (4), dexamethasone (4), paracetamol (4), omeprazole (3), oxycodone (3), sulfamethoxazole-trimethoprim (3), acalabrutinib (2), brentuximab (2), cabozantinib (2), cisplatin (2), esomeprazole (2), ibuprofen (2), indoximod (2), loxoprofen (2), mycophenolic acid (2), nintedanib (2), pomalidomide (2), prednisone (2), simvastatin (2), talimogene (2), tramadol (2), aldesleukin (1), amlodipine (1), amoxicillin (1), atorvastatin (1), axitinib (1), BCG vaccine (1), budesonide (1), candesartan (1), ciprofloxacin (1), clarithromycin (1), clonazepam (1), cobimetinib (1), cortisone (1), crizotinib (1), dacarbazine (1), dalteparin (1), daratumumab (1), eldecalcitol (1), escitalopram (1), eszopiclone (1), ethanol (1), famotidine (1), G-CSF (1), gabapentin (1), hydroxychloroquine (1), infliximab (1), interferon (1), interleukins (1), isoniazid (1), lansoprazole (1), lenalidomide (1), lercanidipine (1), levetiracetam (1), levothyroxine (1), magnesium oxide (1), metamizole (1), metformin (1), olanzapine (1), oxcarbazepine (1), pemetrexed (1), prednisolone (1), risperidone (1), rovalpituzumab tesirine (1), sodium polystyrene sulfonate (1), sultamicillin (1), temozolomide (1), varenicline (1), venlafaxine (1), vonoprazan (1), urelumab (1), zoledronic acid (1).

[c] Arthritis (1), diabetes (2), neuropathy (1), Guillain-Barre syndrome (1), uveitis (1).

diagnosis (viral serology, immune antibody, biopsy, liver imagery) were described. Time to hospitalisation or time to death was not reported. Previous anticancer drugs or whether patients were re-challenging with ICI was not detailed. No information about hepatitis management was given. In the pharmacologic base, co-reported suspected or concomitant drugs are reported and could induce a protopathic bias [18].

Nevertheless, this is a report from a large database that gives the awareness of a clinically relevant complication of ICIs with increasing incidence.

With growing indications of ICIs and development of combination of ICIs with other anticancer hepatotoxic drugs, more cases of hepatitis might be expected. Hepatitis can be a mild adverse event with limited biological abnormalities, but some severe and even fulminant cases can occur. The severity must not be underestimated, patients should be closely monitored and other concomitant hepatotoxic drugs or conditions should be

Table 2
Description of 94 patients' death from immune checkpoint inhibitor–associated hepatitis.

Characteristics	n (%)	Data available, n (%)
Age, years; median, [IQR], (range)	66.5 (58–74.3] (32–88)	78/94 (83)
Male sex	60/90 (67)	90/94 (96)
Indications		
Melanoma	45/79 (57)	79/94 (84)
Lung cancer	25/79 (32)	
Renal cancer	2/79 (2)	
Hepatocellular carcinoma	2/79 (2)	
Other cancers[a]	5/79 (7)	
Treatment		
Monotherapy anti–CTLA-4: ipilimumab	15/94 (16)	All
Monotherapy: anti–PD-1 or anti–PDL-1	55/94 (59)	
Nivolumab	31/55 (56)	
Pembrolizumab	19/55 (35)	
Atezolizumab	5/55 (9)	
Combination: ipilimumab + nivolumab	24/94 (25)	
Time to onset, days; median, [IQR], (range)	41 [20–146] (3–612)	27/94 (29)
Co-reported suspected drugs		
Patients with co-reported suspected drug	18/94 (19)	All
1 co-reported drug	6/18 (33)	
≥2 reported drugs	12/18 (67)	
Carboplatin	4/18 (22)	
Dabrafenib	3/18 (17)	
Paclitaxel	3/18 (17)	
Escitalopram	2/18 (11)	
Omeprazole	2/18 (11)	
Trametinib	2/18 (11)	
Others co-reported suspected drugs[b]	1/18 (6)	
Year of reporting		
2010–2015	13/94 (14)	All
2016	13/94 (14)	
2017	35/94 (37)	
2018	33/94 (35)	
Co-reported irAEs		
Patients with ≥1 irAE	5/94 (5)	All
Myocarditis	4/5 (80)	
Pneumonitis	1/5 (20)	

CTLA-4, cytotoxic T-lymphocyte–associated antigen-4; PD-1, programmed cell death 1; PDL-1, programmed death ligand 1; IQR: interquartile range, irAE: immune-related adverse event.

[a] Bladder, head and neck, lymphoma, neuroendocrine carcinoma, prostate.

[b] Cabozantinib, cisplatin, clonazepam, dacarbazine, dalteparin, dexamethasone, eldecalcitol, ibuprofen, indoximod, interferon, levetiracetam, loxoprofen, metformin, olanzapine, oxcarbazepine, oxycodone, paracetamol, pemetrexed, prednisolone, simvastatin, sulfamethoxazole-trimethoprim, talimogene.

excluded. The management is challenging as corticosteroids can be avoided in some cases of hepatitis [12,19], but more severe cases can be resistant to corticosteroids and would need more aggressive treatment such as plasma exchange [20]. Liver transplantation is contraindicated because of cancer. Hepatitis diagnosis and management should also be conducted with the help of a hepatologist in a multidisciplinary team to avoid a fatal outcome. Moreover, predictive factors of progression to fatal hepatitis are needed.

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Author contributions

A.V. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. D.B.J., B.L.-V., J.J.M. and J.-E.S. contributed to study concept and design. B.L.-V. and J.-E.S. obtained the data. A.V., E.D.M. and J.-E.S contributed to statistical analysis and interpretation of data. A.V., E.D.M. and J.-E.S. contributed to drafting of the manuscript. E.D.M., D.B.J., B.L.-V., J.J.M. and J.-E.S. contributed to critical review of the manuscript for important intellectual content. J.-E.S. contributed to supervision of the study. All authors read and approved the final version for submission.

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Conflict of interest statement

J.J.M. has served on advisory boards at Bristol-Myers, Pfizer, Novartis, Takeda, Regeneron and MyoKardia and has received research funding from Pfizer and Bristol-Myers Squibb. D.B.J. serves on advisory boards for Array BioPharma, BMS, Genoptix, Incyte and Merck and receives research funding from BMS and Incyte. The other authors have no conflict of interest to disclose.

The supplied data from VigiBase come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of Uppsala Monitoring Centre (UMC) or of the World Health Organization (WHO).

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