Journal of Clinical and Translational Hepatology **2022** vol. 10(6) | 1194–1204
DOI: 10.14218/JCTH.2022.00105

Review Article

Immunotherapy-induced Hepatotoxicity: A Review

Teresa Da Cunha, George Y. Wu and Haleh Vaziri*

Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Health Center, Farmington, CT, USA

Received: 1 March 2022 | **Revised:** 18 June 2022 | **Accepted:** 28 June 2022 | **Published:** 22 July 2022

Abstract

Immune checkpoint inhibitors (ICIs) suppress the function of immune checkpoints, which are involved in down-regulating immune responses. These lead to an increased activation of the function of T cells, increased release of cytokines, and decreased activity of regulatory T cells. This allows for a more significant and less regulated immune response and subsequent enhanced cytotoxic activity against cancer cells. A number of cancers are now being treated with these agents and this increased use has resulted in more reports of toxicity. While almost every organ can be affected, the skin, gastrointestinal tract, liver, and endocrine glands are most commonly involved. It is necessary that gastroenterologists and hepatologists familiarize themselves with diagnostic steps and management plan in patients with these undesirable outcomes. When assessing for possible ICIs induced hepatotoxicity, it is of utmost importance to use a formal scoring system such as the Roussel Uclaf causality assessment method (RUCAM) to assess for risk factors, alternative causes, and response to cessation and re-exposure of a given drug. While this review is based on studies with and without RUCAM, the conclusions were carefully established mainly from studies that used RUCAM. The aim of this review is to provide information on the epidemiology, risk factors, clinical presentation, diagnostic tools, and management plan based on the most recent studies of immunotherapy-induced hepatotoxicity.

Citation of this article: Da Cunha T, Wu GY, Vaziri H. Immunotherapy-induced Hepatotoxicity: A Review. J Clin Transl Hepatol 2022;10(6):1194–1204. doi: 10.14218/JCTH.2022.00105.

Introduction

In the past decade, the use of immune checkpoint inhibitors (ICIs) has been increasing because of their promising outcomes in treatment of several types of advanced malignancies compared with chemotherapy.[1] They work by enhancing host antitumor activity by blocking immune checkpoints, which in turn leads to a series of steps at a cellular level that promote proinflammatory events. There are three main classes of ICIs, anti-programmed cell death receptor-1 (PD-1) antibody, anti-programmed cell death ligand-1 (PDL-1) antibody, and anti-cytotoxic T-lymphocyte-associated molecule-4 (CTL-4) antibody. All three classes block the inhibitory effects that immune checkpoints exert on the immune system and consequently allow for a less regulated and increased immune response from a variety of immune cells.

Unfortunately, the overactive immune response may result in some immune-related adverse events.[2,3] The skin, endocrine, respiratory, and the gastrointestinal organs are the most commonly affected. PD-1 and PD-L1 inhibitors are mostly associated with fatigue, rash, hypothyroidism, pneumonitis, and colitis.[3,4] Cutaneous adverse effects have been described as a very common immune side effect of anti-CTL-4 followed by colitis and hypophysitis. However, hepatitis is an important side effect of all three classes of ICIs, as its occurrence often leads to the discontinuation of therapy and might require treatment.[5]

Immunotherapy-induced hepatotoxicity can range from mild elevation of liver aminotransferases to rarely, fulminant liver failure.[6] The reported incidence of immunotherapy-induced hepatitis varies widely, with most clinical trials reporting a low rate around 5.8%.[7] However, some retrospective studies report higher rates of that adverse effect, up to 64%.[8] Moreover, the management of hepatotoxicity recommended by various societies differs among professional societies, and some studies have suggested approaches that diverge from the guidelines.[9–11] This review aims to present the most current data on epidemiology, pathophysiology, clinical presentation, diagnostic tools, and options for management of immunotherapy-induced hepatotoxicity.

ICIs

Mechanisms of action, clinical indications, and common adverse events

Immune checkpoints are molecules that have an important role in the regulation of the immune system. Their function involves the attenuation of T cell activation to particular antigens and allow for prevention of exacerbated immune response and autoimmunity. The process entails recurrent exposure to antigens and consequent decrease in proinflammatory cytokine production, loss of cytotoxic activity,

Keywords: Immune checkpoint inhibitors; Immunotherapy; Hepatitis; Liver injury.

Abbreviations: AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated molecule-4; DILI, drug-induced liver injury; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death ligand-1; RCC, renal cell cancer.

***Correspondence to:** Haleh Vaziri, Department of Gastroenterology and Hepatology, University of Connecticut Health Center, Farmington, CT 06030, USA. ORCID: https://orcid.org/0000-0002-1550-5496. Tel: +1-860-679-6524, Fax: +1-860-679-3159, E-mail: hvaziri@uchc.edu

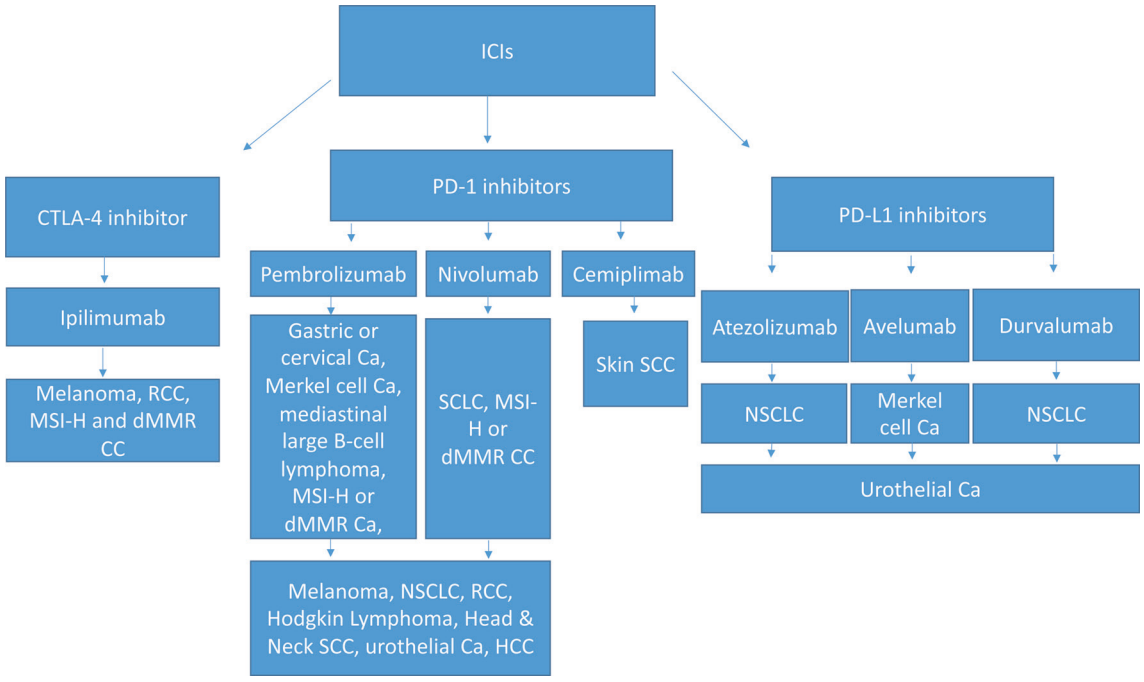

Fig. 1. Immune checkpoint inhibitors and their indications. dMMR CC, deficient mismatch repair deficiency colon cancer; HCC, hepatocellular carcinoma; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.

and decrease in proliferative potential and increased apoptotic activity.[12] ICIs are monoclonal antibodies that target immune checkpoint molecules and are an evolving therapy for late-stage malignant tumors, particularly metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell cancer (RCC), and hepatocellular carcinoma (HCC). The inhibition of immune checkpoints by these agents results in an increased in T cell-specific immune response and consequent antitumor activity.[12] There are three main immunological targeting immune checkpoint molecules including, PD-1, PDL-1, and CTL-4. Ipilimumab (an anti-CTLA-4 antibody) has been approved by the Federal Drug Administration (FDA) for the treatment of melanoma, certain subtypes of colorectal cancer, metastatic NSCLC, HCC, and RCC.[13] Pembrolizumab (an anti-PD-1 antibody) is used in patients with advanced melanoma, NSCLC, head and neck squamous cell cancer, HCC, classical Hodgkin lymphoma, mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high or deficient mismatch repair cancer, gastric cancer, cervical cancer, Merkel-cell carcinoma, RCC. Nivolumab (an anti-PD-1 antibody) is used in the treatment of melanoma, NSCLC, small-cell lung cancer, RCC, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high, deficient mismatch repair colorectal cancer, or HCC.[14–21] Atezolizumab and durvalumab (anti-PDL-1 antibodies) are both used in the treatment of NSCLC and urothelial carcinoma. Avelumab (an anti-PDL-1 antibody) is used for Merkel-cell carcinoma and urothelial carcinoma.[22–25] Figure 1 shows the currently approved ICIs.

In a retrospective study by Bajwa *et al*.,[26] the most common toxicities associated with ICIs were type 1 diabetes (22/139), acute kidney injury (16/139), colitis (14/139), adrenocorticotropic hormone insufficiency (12/139), hepatitis (11/139), myocarditis (10/139), and hypothyroidism (7/139). The mean age of patients presenting with hepatitis was 62 years. Nivolumab was most commonly associated with gastrointestinal toxicities, but a similar frequency of hepatotoxicity was observed in patients taking pembrolizumab and nivolumab. Unfortunately, there was no analysis of male to female ratio or other subgroup analysis.

Pathophysiology

Side effects of ICIs are often related to disproportionate and unregulated immune responses, as seen in autoimmune diseases. That in turn leads to organ damage that may include direct and indirect immune-related cytotoxic effects. PDL-1 is a transmembrane protein expressed in several tissues and tumors. Its role is to protect cells from attack by CD8+ cytotoxic T lymphocytes. PDL-1 binds to PD-1 which is found in T cells, B cells, and myeloid cells and regulates its inhibition. Blockage of PDL-1/PD-1 pathway thus induces cytotoxic activity and confers an immune response toward cancer cells, but also tissue damage through autoimmune responses.[27–29] Moreover, ICIs can also change the properties of CD8+ T cells and make them more prone to undergo synthesis of cytotoxic substances such as interferon gamma (IFN-γ), granzyme, and granulysin.[30] Similarly, CTLA-4 is a receptor located on surfaces of regulatory T cells and activated T cells. After binding to CD80 or CD86 on the surface of antigen presenting cells, it acts as an off switch through inhibitory signals leading to attenuation of T cells function.[28,30] Inhibiting this receptor thus allows for T cell hyperresponsiveness.

Although the mechanism of hepatotoxicity involves an autoimmune process that is a consequence of the inhibition of downregulating mechanisms of the immune system itself, there are differences compared with autoimmune hepatitis (AIH). AIH involves development of specific antibodies that target the liver, whereas in hepatitis associated with ICIs the antibodies are not usually present. Cytotoxic injury from activated and unregulated T cells is thought to be the main mechanism of liver damage. Riveiro-Barciela *et al*.[31] studied the two diseases and found that there was no statistically significant difference in clinical presentation in most cases,

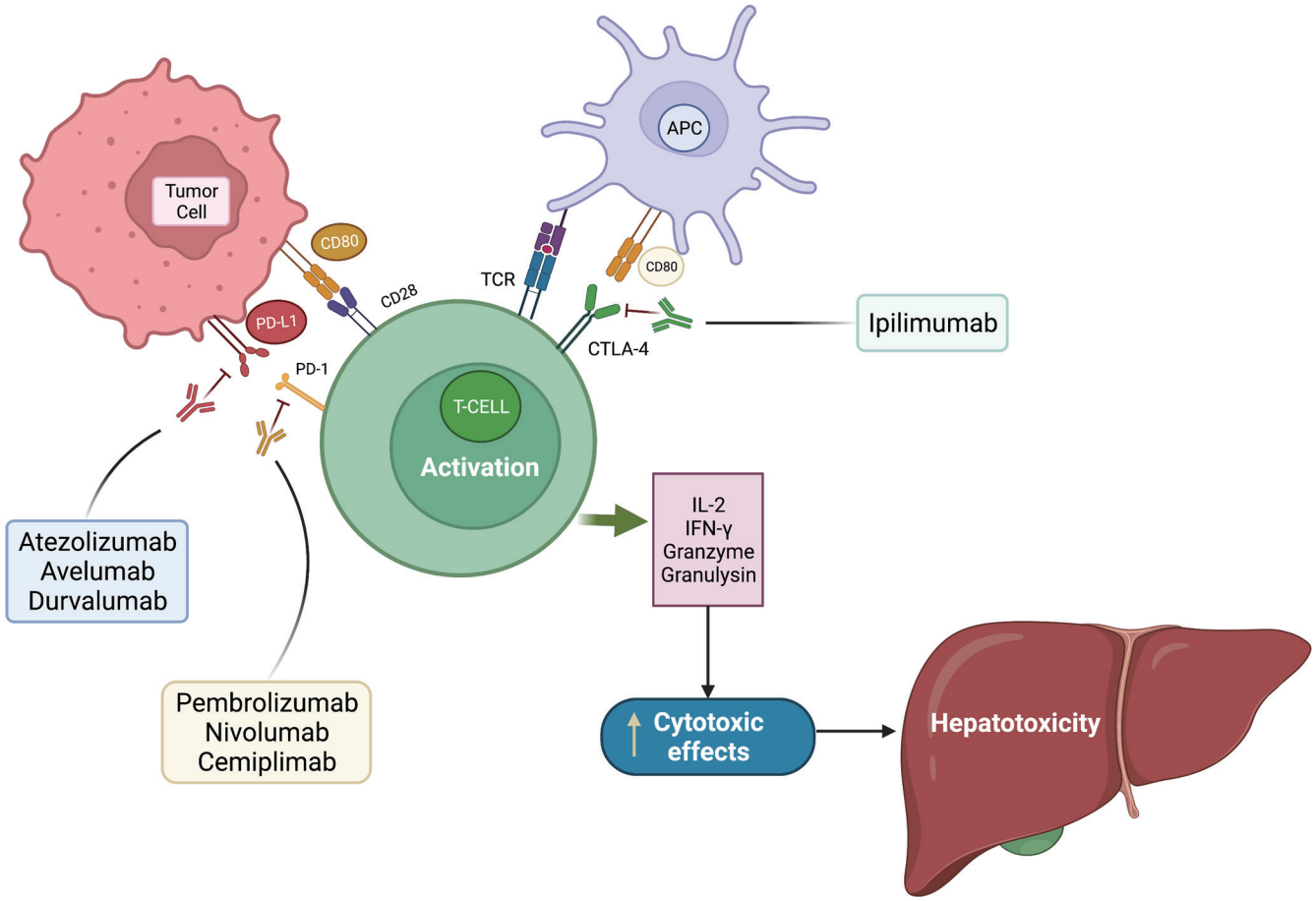

Fig. 2. Illustration of the mechanisms of action of immune checkpoint inhibitors and proposed mechanism of hepatotoxicity. APC, antigen presenting cell; PDL-1, programmed cell death ligand-1; TCR, toll-like receptor; PD-1, programmed cell death receptor-1, CTLA-4, cytotoxic T-lymphocyte-associated molecule-4.

but there was a statistically significant higher incidence in the presence of liver autoantibodies (anti-nuclear antibodies, perinuclear anti-neutrophil cytoplasmic antibodies and anti-smooth muscle antibodies) in AIH compared with ICI-related hepatoxicity. Figure 2 illustrates the mechanisms of action of different ICIs and provides a simple overview of the pathophysiology of immunotherapy-induced hepatotoxicity.

Grading of liver toxicity

Most studies use the Common Terminology Criteria for Adverse Events (CTCAE) for the grading of liver toxicity.[8,9,22–34] A few use the Drug-Induced Liver Injury Network (DILIN) criteria.[35–37]

Table 1 provides an overview of the grading of hepatotoxicity according to both criteria.

Epidemiology

Clinical trials

In a study of 131 patients who were treated with ipilimumab monotherapy for metastatic melanoma, only two (1.5%) developed elevated alanine aminotransferase (ALT) and one (0.8%) had elevated aspartate aminotransferase (AST).[38] None of the patients had grade 3 or higher elevation of aminotransferases. In a randomized, controlled phase 3 study of 834 patients with advanced melanoma, patients were divided into three groups at a 1:1:1 ratio to receive pembrolizumab (10 mg/kg) every 2 weeks, or every 3 weeks, or four doses of ipilimumab every 3 weeks (3 mg/kg).[4] Hepatitis occurred in 1.1%, 1.8%, and 1.2% of the patients, respectively. All patients in the pembrolizumab group had grade 3 to 5 hepatitis compared with only 0.4% in the ipilimumab group, based on the CTCAE grading system (Table 1). There were no significant differences in the demographic and disease characteristics between the groups. However, the baseline liver tests prior to the treatment were not provided in this study.

Weber *et al*.[39] compared adjuvant nivolumab (3 mg/kg every 2 weeks) and ipilimumab (10 mg/kg every 3 weeks) in patients with resected advanced melanoma. There were 453 patients in each therapy group with no significant difference in demographic and clinical characteristics between the groups. ALT was elevated in 6.2% in the nivolumab group and 14.6% in the ipilimumab one. In addition, grade 3–4 elevation of ALT was seen in 1.1% and 5.7% of patients, respectively, whereas that for AST was reported in 0.4% and 4.2%, respectively. Resolution of liver injury occurred within 3–6 weeks. Similar to previous studies, the authors did not report the baseline liver tests and whether other causes for hepatotoxicity had been ruled out. Another study evaluated the use of pembrolizumab at different doses (either 2 mg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) for treatment of NSCLC in 495 patients.[40]

Table 1. Grading of hepatotoxicity by the drug-induced liver injury network and common terminology criteria of adverse events

Grade	Drug-induced liver injury network	Common terminology criteria of adverse events
GRADE 1	AST and/or ALP levels are elevated; total serum bilirubin <2.5 mg/dL and no coagulopathy (INR <1.5)	ALT and/or AST > ULN - 3.0 × ULN; 1.5–3.0 × baseline if baseline was outside normal range. ALP > ULN - 2.5 × ULN; 2.0–2.5 × baseline if baseline was outside normal range. TBILI > ULN - 1.5 × ULN; > 1.0–1.5 × baseline if baseline was outside normal ranges.
GRADE 2	The AST and/or ALP levels are elevated; total serum bilirubin level ≥2.5 mg/dL or coagulopathy (INR ≥1.5) without elevated bilirubin	ALT and/or AST > 3.0–5.0 × ULN; > 3.0–5.0 × baseline if baseline was outside normal range. ALP > 2.5–5.0 × ULN; > 2.5–5.0 × baseline if baseline was outside normal range. TBILI > 1.5–3.0 × ULN; > 1.5–3.0 × baseline if baseline was outside normal range.
GRADE 3	the AST and/or ALP levels are elevated; total serum bilirubin level ≥2.5 mg/dL and prolonged hospitalization due to drug-induced liver injury	ALT and/or ALT > 5.0–20.0 × ULN; > 5.0–20.0 × baseline if baseline was outside normal range. ALP > 5.0–20.0 × ULN; > 5.0–20.0 × baseline if baseline was outside normal range. TBILI > 3.0–10.0 × ULN; > 3.0–10.0 × baseline if baseline was outside normal range.
GRADE 4	the AST and/or ALP levels are elevated; total serum bilirubin level ≥2.5 mg/dL and one of the following: signs of hepatic decompensation (INR ≥1.5, ascites, encephalopathy), or other organ failure	ALT and/or ALT > 20.0 × ULN; > 20.0 × baseline if baseline was outside normal range. ALP > 20.0 × ULN; > 20.0 × baseline if baseline was outside normal range. TBILI > 10.0 × ULN; > 10.0 × baseline if baseline was outside normal range.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal; TBILI, total bilirubin.

Fifteen patients (3%) had an elevated AST of any degree and three (0.6%) had grade 3 to 5 elevated AST. No difference was seen in the overall adverse effects among different therapy doses. However, the authors did not specify the AST levels corresponding to each treatment dose group. In a randomized, double-blind, phase 3 study 945 patients with advanced melanoma were assigned in a 1:1:1 ratio to treatment with nivolumab monotherapy (3 mg/kg every 2 weeks), nivolumab plus ipilimumab (nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond) or ipilimumab monotherapy (ipilimumab 3 mg/kg every 3 weeks for four doses).[15] Elevated ALT of any grade was observed in 3.8%, 17.6%, and 3.9%, with grade 3 or 4 elevated ALT in 1.3%, 8.3%, and 1.6%, respectively. Moreover, elevated AST was seen in 3.8%, 15.3%, and 3.5%, with grade 3–4 elevated AST in 1%, 6.1% and 0.6%, respectively. Resolution of liver injury occurred within 4–7 weeks. Unfortunately, the article did not specify at which time during treatment the hepatotoxicity occurred.

A randomized cohort study evaluated 147 patients with recurrent small cell lung cancer treated with nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles followed by nivolumab 3 mg/kg every 2 weeks.[41] Seven patients (4.8%) in the nivolumab monotherapy group had elevated AST of which two (1.4%) were grade 3–4. In this group, ALT was only increased in four patients (2.7%) and all were less than grade 3. Ten patients (10.4%) in the combination therapy group had any grade of elevated AST, with five patients (5.2%) graded as 3–4. In that group, ALT was elevated in nine patients (9.4%) with five (5.2%) having grade 3–4. Although the authors reported that a total of 112 patients had liver metastasis, they did not correlate it with the occurrence of hepatotoxicity. A large systematic review by Chang *et al*.[42] of phase 2 and 3 randomized clinical trials included a total of 5,051 patients. Their results showed that ipilimumab 3 mg/kg every 3 weeks conferred the lowest risk of hepatotoxicity compared with nivolumab and dual therapy. Furthermore, nivolumab 1 mg/kg every 3 weeks combined with ipilimumab 3 mg/kg every 3 weeks was associated with a higher risk of any increase or severe increase in ALT and severe increase in AST. Other studies have reported grade 3–4 hepatotoxicity with a frequency of 1.4–11%.[7,8] In a meta-analysis of 117 trials and 22,006 patients, 5.88% had elevated AST, 5.29% had elevated ALT, and only 1.21% had elevated bilirubin levels. The overall incidence of immunotherapy-related hepatitis was 1.24%, with 0.9% having high-grade hepatitis. Other hepatic disorders included elevated alkaline phosphatase (3.19%), elevated gamma-glutamyl transferase (1.85%) and hepatobiliary disorders (2.28%).[7] The study had an adequate power given the large sample size. However, it analyzed independently published studies, which increased the risk of publication bias. Table 2 summarizes the incidence of immunotherapy-induced hepatotoxicity of different trials according to each type of immune checkpoint inhibitor.[4,15,24,38–41,43–45]

Another retrospective study evaluated 194 patients in two centers over the course of 3 years.[8] Of the 194 patients, 125 (64.4%) developed hepatotoxicity. A total of 37 (29.6%) patients were women and 88 (70.4%) were men. The incidence of hepatotoxicity decreased with advancing age, as 16 (80%) patients between 30 and 50 years of age had hepatotoxicity, compared with 72 (72%) of those between 50 and 70 years of age and 37 (50%) of those who were more than 70 years of age. The results were statistically significant, but there was no analysis of hepatotoxicity according to the type of ICI administered. On the other hand, a retrospective study by Tsung *et al*.,[35] found no statistically significant differences in the mean age of patients with ICI-induced liver injury compared with those without liver injury. However, the authors did not perform a subgroup analysis according to age group. In that study the overall incidence of liver injury was 14.3% (70 of 491 patients treated with pembrolizumab). Importantly, only 20 cases (28.6%) were adjudicated as probably related to ICI treatment based on the Roussel Uclaf causality assessment method (RUCAM). Another study evaluated 576 nivolum-

Table 2. Incidence of hepatotoxicity according to different treatment regimens with immune check point inhibitors reported by different studies

Therapy	Author	Patients, *n*	Therapy dose	Elevated AST, *n* (%)		Elevated ALT, *n* (%)	
				All grades	Grade 3 or >	All grades	Grade 3 or >
Ipilimumab	Hodi *et al*.[38]	131	3 mg/kg every 3 weeks for four doses	1 (0.8)	0 (0)	2 (1.5)	0 (0)
	Robert *et al*.[4]	256	3 mg/kg every 3 weeks	6 (2.3)	2 (0.8)	9 (3.5)	2 (0.8)
	Weber *et al*.[38]	453	10 mg/kg every 3 weeks	60 (13.2)	19 (4.2)	66 (14.6)	26 (5.7)
	Larkin *et al*.[15]	311	3 mg/kg every 3 weeks for four doses	11 (3.5)	2 (0.6)	12 (3.9)	5 (1.6)
Nivolumab	Weber *et al*.[38]	452	3 mg/kg every 2 weeks	25 (5.5)	2 (0.4)	28 (6.2)	5 (1.1)
	Larkin *et al*.[15]	313	3 mg/kg every 2 weeks	12 (3.8)	3 (1.0)	12 (3.8)	4 (1.3)
	Ready *et al*.[41]	147	3 mg/kg every 2 weeks	7 (4.8)	2 (1.4)	4 (2.7)	0
	Motzer *et al*.[43]	59	0.3 mg/kg every 3 weeks	2 (3)	1 (2)	2 (3)	1 (2)
	Motzer *et al*.[43]	54	2 mg/kg every 3 weeks	4 (7)	1 (2)	2 (4)	1 (2)
	Motzer *et al*.[43]	54	10 mg/kg every 3 weeks	2 (4)	0 (0)	3 (6)	0 (0)
Pembrolizumab	Robert *et al*.[4]	278	10 mg/kg every 2 weeks	14 (5)	0 (0)	12 (4.3)	0 (0)
	Robert *et al*.[4]	277	10 mg/kg every 3 weeks	6 (2.2)	1 (0.4)	4 (1.4)	1 (0.4)
	Garon *et al*.[40]	495	10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks				
	Andre *et al*.[24]	153	200 mg every 3 weeks	24 (16)	4 (3)	22 (14)	4 (3)
Nivolumab plus ipilimumab	Larkin *et al*.[15]	313	1 mg nivolumab/kg every 3 weeks plus 3 mg ipilimumab/kg every 3 weeks for four doses, followed by 3 mg nivolumab/kg every 2 weeks for cycle 3 and beyond	48 (15.3)	19 (6.1)	55 (17.6)	26 (8.3)
	Ready *et al*.[41]	96	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles followed by nivolumab 3 mg/kg every 2 weeks	10 (10.4)	5 (5.2)	9 (9.4)	5 (5.2)
Pembrolizumab plus Ipilimumab	Long *et al*.[44]	153	Pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by pembrolizumab 2 mg/kg every 3 weeks for up to 2 years	17 (11)	0 (0)	15 (10)	3 (2)
	Boyer *et al*.[45]	282	Pembrolizumab 200 mg every 3 weeks for up to 35 doses plus ipilimumab 1 mg/kg every 6 weeks for up to 18 doses	36 (12.8)	5 (1.8)	32 (11.3)	9 (3.2)

ab-treated patients, of whom, 71% experienced therapy related adverse events. While up to 2.8% of patients had elevated AST, hepatitis was only seen in 0.2% of the patients and was regarded as grade 3–4 following the CTCAE (Table 1).[33] Unfortunately there was no subgroup analysis of the patients that developed hepatotoxicity. An incidence of 4.6% of immunotherapy-related hepatotoxicity (21 of 453 patients) was reported in another retrospective study.[9]

Significant differences in the reported incidence rates of ICI-induced hepatotoxicity in various studies may be the re-

sult of two main factors. The first is the type of ICI therapy being studied. As mentioned previously, some studies only analyzed patients who were treated with an anti-PD-1,[35] while others included all therapies and did not report incidence rates according to the type of therapy.[8] The second factor is how hepatotoxicity was defined in different studies. For example, some studies used DILIN study criteria[35,36] and others defined the hepatotoxicity based on the CTCAE,[8,9,22,33,34] which provides different grading numbers according to the severity of liver injury. Some studies did not report any specific criteria for hepatotoxicity.[7,46] Importantly, the two grading systems have significantly different thresholds for including or excluding patients. (Table 1)

A meta-analysis by Wang *et al*.[6] investigated the fatality rates associated with ICIs. Of 31,059 individuals who were treated with ICIs, a total of 613 fatal cases directly related to side effects of ICIs were reported. Of the 613 cases, 124 (20.2%) were secondary to hepatitis. The authors also assessed fatality rates of different classes of toxic effects and identified a risk of hepatitis-related deaths ranging from 10% to 17% of reported cases. In their study, the risk of fatality secondary to hepatitis differed according to the type of therapy, and the risk was higher in those taking anti-PD-1/PD-L1. Of all patients dying from hepatitis, 31 (25%) received ipilimumab, 74 (59.7%) received anti-PD-1/PD-L1, and 19 (15.3%) had a combination of the two types of therapy (anti-CTLA-4 and anti-PD-1/PD-L1). When comparing all causes of death according to type of therapy, hepatitis was responsible for 16% of the deaths in the ipilimumab group, 22% in the anti-PD-1/PD-L1 monotherapy, and 22% in the combination therapy group. The authors also analyzed 3,545 patients who were treated for melanoma in seven large international academic centers. Twenty-one deaths related to ICIs toxicities were reported, of which five (23.8%) were related to hepatitis.[6] The median age of patients dying from all causes of toxic effects was 70 years compared with an average of 62 years in patients with non-fatal toxicities.

Risk factors

Several risk factors have been reported to predispose patients to ICI-induced hepatotoxicity. In a retrospective study, multivariate analysis found that acetaminophen intake increased the risk of hepatotoxicity by 2.1 times with an attributable risk of 53.2%.[8] However, the study was limited by its retrospective nature and lack of data on the doses of acetaminophen that were used. The severity of hepatotoxicity has been reported to be higher in patients treated with ICIs for primary liver cancer. A large meta-analysis by Fu *et al.*[7] showed that patients with primary liver cancer had significantly higher incidences of elevated ALT (4.57% vs. 1.26%), AST (6.74% vs. 1.19%), bilirubin (3.06% vs. 0.62%), and hepatobiliary disorders (2.78% vs. 1.57%) than other solid tumors. The incidence of grade 3 or higher hepatotoxicity was also significantly higher in primary liver cancer than in other solid tumors, but there were no data regarding the liver tests of the patients prior to the start of immunotherapy. CTCAE hepatotoxicity grading is based on the proportion of elevated transaminases compared with baseline. Patients with HCC already have a high risk of elevated aminotransferases because of tumor and bystander necrosis, but the study did not report whether hepatotoxicity severity grading took that into account.

HMG-CoA reductase inhibitors may also increase the risk of ICI-hepatotoxicity. Cho *et al*.[8] reported an increased association of the use of HMG-CoA reductase inhibitors and development of ICI-induced hepatitis, with a 4.7-fold increased risk and an attributable risk of 78.8%. Of note, the authors did not include patients with elevated baseline AST or ALT. As mentioned previously, the presence of hepatic metastases has a significant impact on the likelihood of ICI-induced hepatotoxicity. Tsung *et al*.[35] reported that hepatic metastasis was more common in those with ICI compared with those without liver injury (53% vs. 21%, $p<0.01$). No association was reported between the risk of hepatotoxicity and the number of doses of ICIs that the patients had received. Hepatitis was reported after only one dose and more than 17 doses.[26] Cho *et al*.[8] reported a median time from initiation of therapy to hepatotoxicity of 24 days, but the time was significantly shorted in men (29 days) than in women (49 days). In addition, the median time in patients who were 65 years of age or younger was 25 days compared with 42 days in those more than 65 years of age, but the difference was not statistically significant. In addition, increased doses of ipilimumab (10 mg/kg vs. 3 mg/kg) have been associated with more severe liver injury and higher fatality.[6,47] While there are no specific data regarding viral hepatitis and concomitant use of ICIs, a synergistic hepatotoxic effect has been seen in combination with drug-induced liver injury, and thus screening for viral hepatitis prior to initiation of ICIs, and prophylactic treatment of positive patients is an important consideration.[48]

Clinical features

Hepatotoxicity associated with ICIs is frequently characterized by elevation of aminotransferases including, AST and ALT, and less often by hyperbilirubinemia. The onset of hepatotoxicity varies significantly with the type of therapy. It has been reported to occur sooner with anti-CTLA-4, starting 1–7 weeks (average of 3 weeks) after initiation of therapy compared with 2 to 49 weeks (average of 14 weeks) in patients receiving anti-PD-1/PD-L1.[49] Some patients are asymptomatic. However, fever, jaundice, fatigue, and a maculopapular rash have been reported.[49–52] Although the clinical features were present at the time of hepatotoxicity, some may have represented an ICI side effect unrelated to hepatotoxicity. Moreover, other immunotherapy-induced adverse effects are common, including pneumonitis, bronchitis, hyperthyroiditis, hypophysitis, and pancreatitis.[49] The degree of elevation of aminotransferases is usually higher in patients who are symptomatic compared with those without symptoms.[51] The pattern of liver injury tends to be hepatocellular, although cholestatic and mixed patterns have been observed.[53] The presence of cholestatic injury is reported to be more associated with the presence of liver metastases.[35] In a study of 536 patients receiving ICIs, 19 developed grade 3 or higher hepatotoxicity. Three were excluded from the analysis because of remaining cofounding factors, 16 were included. Peak AST levels were reported to be as high as 2,289 U/L, and to average around 400 U/L. ALT levels peaked at 3,137 U/L and averaged 460 U/L.[49] There was no significant difference in aminotransferase levels according to type of therapy. Of note, all except for one patient in that study with a gamma-glutamyl transferase of 104I U/L had liver tests within the normal range before initiation of immunotherapy. Wang *et al*.[6] reported that fatal cases tended to result from fulminant hepatic failure, and 80% of fatalities were caused by acute disease. Fortunately, the fatality rate of fulminant liver failure (21 of 3,545 patients, 0.6%) was low.

Severity of hepatotoxicity according to type of therapy

The degree and frequency of liver involvement as a side effect of treatment with ICIs differs between patients treated with CTLA-4 compared with PDL-1 and PD-1 inhibi-

tors.[5,36,52,54] Several studies reported higher frequencies of hepatotoxicity in patients treated with anti-PD-1 inhibitors, and a higher frequencies of severe hepatitis in those treated with anti-CTLA-4 and combination therapies.[5,49,52,55] A systematic review of hepatoxicity in 17 trials of ICIs found that odds ratio for all-grade hepatotoxicity was lower in patients receiving CTLA-4 inhibitors than in those who received PD-1 inhibitors (1.24 vs. 1.52) and that high-grade hepatotoxicity was higher in the anti-CTLA-4 group (1.93 vs. 0.48, respectively).[56] Cheung *et al*.[9] found that 21 of 453 patients treated with ICIs developed ICI-induced hepatotoxicity. Of those, five (23.8%) received anti-PD-1 monotherapy, four (19%) received ipilimumab monotherapy, and 11 patients (52.4%) had combination therapy. Moreover, 75% of patients with grade 4 hepatitis received ipilimumab.

Significantly higher elevations of ALT and AST have been reported with anti-PD-1 (6.01% and 6.84%) than with anti-PDL-1 (3.60% and 3.72%).[7] The results were observed in a meta-analysis that included significantly more patients than Cheung *et al*.[9] but evaluated individual studies. In another large meta-analysis, the incidences of all-grade and grade ≥ 3 hepatitis after combination treatment with pembrolizumab and ipilimumab was 9.8% and 5.9%, respectively. For patients taking a combination of nivolumab and ipilimumab the rates were 4.9% and 3.5%, respectively. Those with nivolumab monotherapy had an incidence of all-grade hepatitis of 3%.[5] Furthermore, the severity of ipilimumab related hepatotoxicity has been shown to be directly related to treatment dose. Doses of 10 mg/kg of ipilimumab were associated with grade 3–4 hepatotoxicity, but doses up to 3 mg/kg may not cause liver injury.[47]

Imaging findings

Imaging findings are nonspecific and often correlate with the severity of hepatitis, which reflects the degree of aminotransferase elevation.[57–60] The most common liver findings on computed tomography (CT) include hepatomegaly, periportal edema, and periportal lymphadenopathy. Nonetheless, a normal hepatobiliary system has also been described on imaging.[51] In a retrospective study of 147 patients treated with ipilimumab for advanced melanoma, three had radiological evidence of liver involvement on CT scans with contrast. CT was characterized by heterogeneous parenchymal enhancement with low-attenuation areas, periportal and gallbladder edema, and ascites. Two patients also had hepatomegaly on imaging. None of the three patients had underlying liver disease or risk factors, including viral infection or exposure to other hepatotoxic drugs or alcohol.[61] The studies did not report the use of RUCAM for the diagnosis of ICI-induced hepatotoxicity.

Histopathology findings

Immunotherapy-induced hepatitis is often established by liver chemistries and after other causes of hepatitis have been ruled out, which precludes the need of a liver biopsy.[9] There are few data of the histological appearance of the liver during the acute phase of hepatotoxicity, as most patients do not undergo liver biopsy. Findings of the reported cases include severe panlobular hepatitis with foci of confluent necrosis, periportal inflammation, and prominent perivenular infiltrate with endothelialitis, and rarely, cholestatic injury.[50,51,62] Inflammatory cells mainly consist of lymphocytes, with a predominance of CD8+ T cells and less frequently CD4+ T cells and B cells. Interestingly, the presence of eosinophils is common, and plasma cells are rare (a distinguishing feature of AIH). Granulomatous hepatitis has also been reported.[50]

A retrospective study by Cohen *et al*.[53] found that 60 patients with ICIs and liver biopsies over the course of 4 years had elevated liver tests that were thought to be secondary to immunotherapy. The mean age was 61 years, and there was no difference in the male to female ratio. Twenty-eight (47%) of the 60 biopsies revealed a predominantly hepatitic pattern of injury consisting of mild to moderate lobular injury in most cases, but severe in six. The most common injury zone was centrilobular or centrilobular predominant (17 biopsies, 36%), followed by azonal (eight biopsies, 13.3%) and panlobular (two biopsies, 3.3%). Lobular inflammation included mainly histiocytes and admixed lymphocytes; scattered plasma cells were seen in five cases, and scattered eosinophils were seen in two cases. Some degree of portal inflammation with granulomas was seen in 11 (39%) of the 28 biopsies, mostly located in zone 3. In 16 cases (26%), there was a cholangitic pattern of injury that was characterized by marked ductal injury with or without portal edema. In 11 of those cases, the portal inflammation included neutrophils surrounding injured ducts. In two cases, the inflammatory components included mononuclear cells with or without eosinophils. In three patients the biopsy findings were identical to nonalcoholic fatty liver disease. In five cases, the changes were mild and nonspecific. The results suggest that while there are a variety of liver injury patterns, the most common type of liver injury associated with ICIs is the hepatocellular pattern. In patients with a portal-based cholangitic pattern, the causes of hepatotoxicity were possibly attributed to liver disease progression in six, concomitant use of chemotherapy in three, sepsis in two, and antibiotic use in two. It is difficult to conclude that all the patients had ICI-related hepatotoxicity, particularly in those with a cholangitic pattern. Nonetheless, the study demonstrated that in patients with presumed ICI-induced hepatotoxicity, the type of liver injury shown by the biopsy results did not change their management, and most patients still needed steroid treatment. Moreover, some of the patients may have had underlying liver disease that impacted the biopsy results.

Another study analyzed liver biopsies from patients with advanced malignancies treated with anti-PD-1 therapy (nivolumab or pembrolizumab).[62] Six of eight patients had acute lobular hepatitis. The inflammation was mild and consisted of a mixed inflammatory cell infiltrate with lymphocyte predominance and few plasma cells and eosinophils. Five cases had spotty necrosis and acidophil bodies, and one had centrilobular necrosis. None of the six cases of lobular hepatitis had significant inflammation or fibrosis in the portal tracts. One patient had steatohepatitis with severe large-droplet macrovesicular hepatitis and mild lobular inflammation. This patient had a prior history of liver steatosis. Another patient had a cholestatic pattern of injury with diffuse bile-duct injury in all portal tracts and mixed canalicular and hepatocellular cholestasis. Patients other than the one with steatohepatitis and a previous history of liver steatosis had normal liver tests prior to treatment. Viral hepatitis panels were negative before and after treatment.

Differential diagnosis

The differential diagnosis of elevated liver tests is broad, and careful evaluation is warranted before concluding that ICIs caused the liver damage. As with other causes of drug-induced liver injury (DILI), it is important to assess causality using the RUCAM scoring system,[63] which considers the time to onset after the beginning of drug treatment, the course of ALT and/or ALP after drug cessation, alcohol use, age, concomitant drugs, alternative causes, and re-

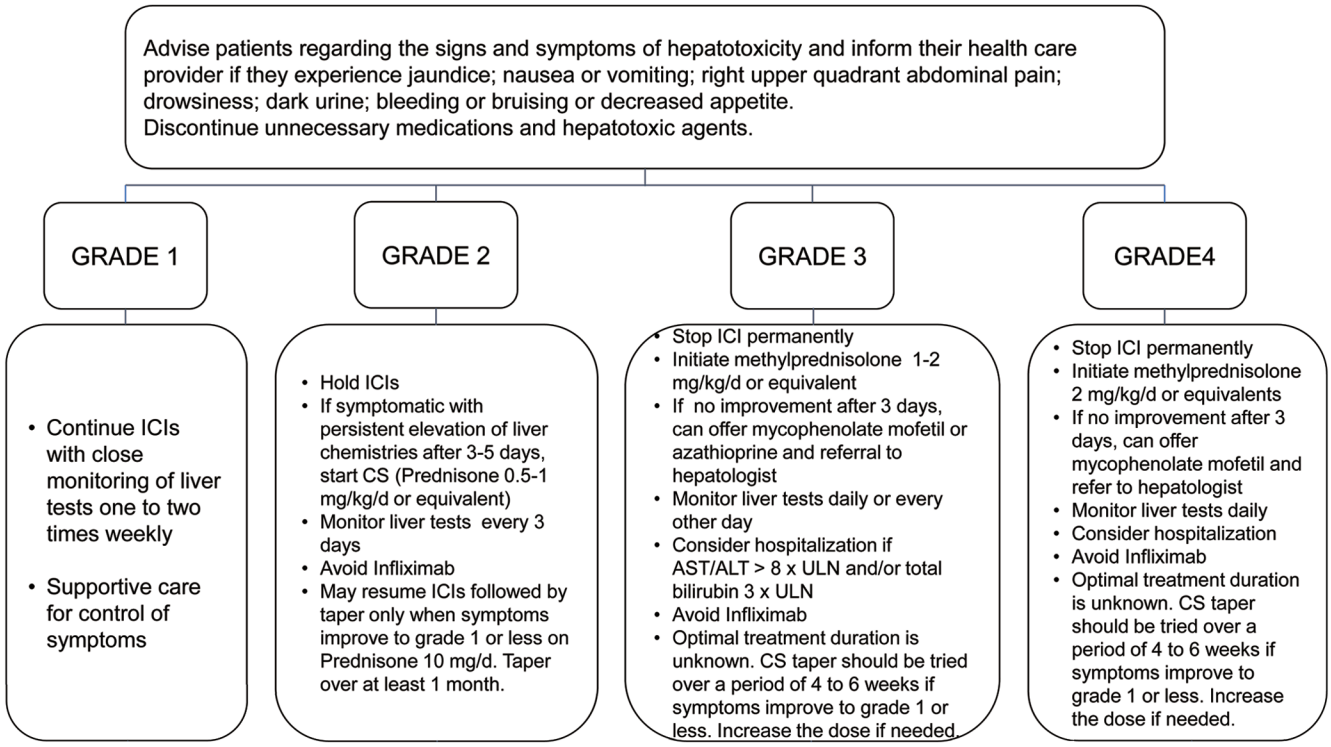

Fig. 3. American Society of Clinical Oncology management of immunotherapy-induced hepatotoxicity. ICI, immune checkpoint inhibitor; CS, corticosteroid.

sponse to drug re-exposure. Nonetheless, many cases that are labeled as DILI may in fact be secondary to alternative causes.[64] This is important because liver metastases, concurrent chemotherapy and the use of other drugs are often present in patients with advanced cancer.[8,35]

Liver injury is most often characterized by a hepatocellular pattern with mild to moderate elevation of liver aminotransferases with marked elevation of the enzymes being less common. For that reason, common etiologies including viral hepatitis including hepatitis A, B, and C, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, autoimmune hepatitis, hepatic steatosis, ischemic hepatitis, biliary disease, and other drug- or herb-induced toxicities are included in the differential diagnosis.[51,63] As mentioned earlier, liver metastasis increases the risk of ICI-induced hepatotoxicity, but its presence might be the sole cause of liver injury.[35]

Management and prognosis

The treatment of immunotherapy-induced hepatotoxicity varies with the severity of hepatitis.[65] Several consensus-based management guidelines proposed by societies recommend that all patients should be evaluated for other causes of hepatitis, and that the steroids should be considered the first line treatment.[66–70]

Investigation of other causes of hepatitis include a workup for viral hepatitis including history of alcohol use, iron stores, and liver imaging for evaluation of potential liver metastasis. A workup for autoimmune hepatitis should also be considered. The American Society of Clinical Oncology guidelines require close monitoring of liver tests prior to each infusion and/or weekly for patients with grade 1 hepatitis (Fig. 3).[70] In grade 2 hepatitis, ICIs should be withheld temporarily, but may be restarted following recovery to grade 1 or less while taking prednisone ≤7.5–10 mg/day. Corticosteroid therapy with prednisone 0.5–1 mg/kg/day (or equivalent) should be started. In addition, more frequent monitoring should be done in patients with no improvement after 5 days. In patients with grade 3 hepatotoxicity, ICIs should be permanently discontinued, and prednisone 1–2 mg/kg/day or methylprednisolone 1–2 mg/kg prescribed. Steroids should be tapered over a course of 4 weeks in patients with improvement of liver tests. In refractory cases, a second agent such as mycophenolate or azathioprine should be considered. Grade 4 toxicity is managed much like grade 3, but methylprednisolone 2 mg/kg may be considered. Liver imaging and biopsy may be considered in patients with grade 3 and 4 hepatitis to assess for alternative causes.

Despite the recommendations made by society guidelines on steroid use in patients with grade 3–4 ICI-induced hepatotoxicity, a systematic review by Peeraphatdit *et al*.[22] found that almost half of these patients improved without requiring corticosteroids.[10,49] The time for complete recovery of liver function after the start of corticosteroids varies widely and may be affected by several factors including the severity of hepatotoxicity, the presence of liver metastases, the type of immunotherapy received, and the time to onset of hepatotoxicity.[9,22,71] A case series described by Gauci *et al*.[10] included five patients with grade 2 or higher hepatotoxicity who did not receive corticosteroids and achieved resolution of liver function sooner than five other patients with a similar presentation who received corticosteroids. The mean recovery of liver function was 4.7 weeks without steroids and 8.6 weeks with steroids. The authors did not report the treatment associated with grade of hepatotoxicity experienced by each patient. They reported that of a total of 10 patients, only 1 had grade 2 hepatotoxicity and the others had grade 3 or higher. Another study reported an average of 3.3 weeks for the resolution of liver injury af-

ter initiation of corticosteroids.[33] Importantly, prednisolone doses > 60 mg/day did not correlate with faster improvement or better outcomes.[9] Moreover, a case report of liver-directed topical budesonide had promising effects.[65]

One study reported that dual immunosuppressive therapy decreased recovery time. Although society guidelines argue against the use of infliximab because of potential hepatotoxic effects, Cheung *et al*.[9] found that steroid-sparing agents including mycophenolate and either tacrolimus or infliximab (two patients, one with hepatitis and one with colitis) improved hepatitis in patients who did not respond to monotherapy with steroids. However, larger studies are needed to investigate the risks and benefits of the use of these immunosuppressors. The use of anti-thymocyte globulin with or without concomitant use of N-acetylcysteine has been reported successful in specific cases of decompensated liver failure when the use of dual immunosuppression was not effective, and/or liver function was rapidly deteriorating. In all the reported cases, rapid improvement of liver function was observed within 24 h of treatment with anti-thymocyte globulin.[72–75]

Preventive measures

There are no specific measures to prevent immunotherapy-induced hepatotoxicity. However, it is important to understand which patients are at increased risk of developing liver injury. Obtaining baseline LFTs before initiation of therapy is encouraged as a standard measure. However, other aspects need to be considered. Patients with primary liver disease, liver metastases, and hepatobiliary disorders are at increased risk of hepatotoxicity.[7,35] Patients taking HMG-CoA reductase inhibitors or acetaminophen may also be at increased risk.[8] Although we did not find any study reporting the use of immunotherapy specifically in patients with underlying chronic viral hepatitis infection, HBV, and HCV have been associated with poorer outcomes in patients with DILI.[76] For that reason, screening patients at increased risk of infection with those viruses should be considered before starting immunotherapy. Alcohol use and hepatic steatosis are considered risk factors for DILI.[76] In such patients, monotherapy rather than dual therapy might be a consideration, although, no data is available to confirm that. Another consideration would be opting for lower doses of therapy. Lastly, more frequent monitoring of liver tests might prevent the development of higher grades of hepatotoxicity if treatment is suspended early.

Retreatment

Restarting therapy with ICIs after liver toxicity occurs is controversial and should be individualized by carefully weighting the benefits and risks. In addition, risk factors that could contribute to liver injury should be carefully investigated before restarting therapy. Most society guidelines recommend continuation of therapy for grade 1 toxicity, re-challenging of therapy if LFTs improve in grade 2 toxicity, and permanent discontinuation of therapy for grade 3 and 4 patients. However, studies have shown tolerance of retreatment with ICIs even with grade 3 hepatotoxicity.[9]

Interestingly, in a study by Cheung *et al*.[9] four patients treated with combination therapy and developed hepatotoxicity were then given up to 19 cycles of nivolumab monotherapy after normalization of aminotransferases without further evidence of hepatotoxicity. Of note, two of the patients had grade 3 hepatotoxicity. Another study reported safe resumption of ICI therapy with concomitant budesonide treatment in two patients who had developed grade 3 hepatitis.[11] As mentioned previously, patients who develop ICI-induced hepatotoxicity while on combination therapy, should only be re-challenged after normalization of liver tests and using monotherapy with either nivolumab or pembrolizumab.[9]

Conclusions

Over the past years there has been increasing information concerning immunotherapy and its detrimental effects on the liver. Generally, clinical trials recorded rates of hepatotoxicity of up to 15%, while retrospective studies have reported up to 64%.[8,15] A major reason for these differences is the use of different grading systems for the description of hepatotoxicity and lack of mention of which system was used.[8,35]

The evidence of clinical trials indicates that there is a higher incidence of hepatotoxicity in patients being treated with combination therapy that with monotherapy. Of all the types of therapies, ipilimumab confers a higher risk of hepatotoxicity and higher fatality rates when given at high doses.[6,47] Moreover, several studies reported different incidences of hepatotoxicity associated with the various therapies.[4,39] Nonetheless, there is a consensus that ipilimumab and combination therapies have the highest risk of high-grade hepatotoxicity.[5,36,52,54] However, the trials did not report the use of RUCAM when assessing for hepatotoxicity. In addition, important identified risk factors associated with higher rates of hepatotoxicity are the use of acetaminophen, HMG-CoA reductase inhibitors, primary liver cancer, and the presence of hepatic metASTasis.[7,8,35] The onset of hepatotoxicity varies widely, but is thought to occur earlier after the use of anti-CTLA-4 compared with either anti-PD-1/PD-L1.[49]

The symptomatology is also broad and sometimes nonspecific, with some patients being asymptomatic and others presenting with fatigue, jaundice and/or maculopapular rash. Moreover, a hepatocellular pattern of liver injury is characteristic, and a cholestatic pattern may rarely occur.[49,50] Fulminant hepatitis has been reported, and usually leads to death, but the overall mortality rate is low and estimated as around 0.1%.[6] In addition, imaging and histopathological findings are generally nonspecific but should be considered to eliminate other causes of liver injury.[50,57–60] The management recommendations of different societies are similar.[66–70] Corticosteroids are recommended to treat grade 2 or higher hepatotoxicity, watchful waiting has resulted in good outcomes.[10] In addition, restarting immunotherapy after grade 3 hepatotoxicity should be performed on an individual basis, but when possible, with a different regimen.

In conclusion, while immunotherapy-induced hepatotoxicity is not common, more cases are being diagnosed given the expanding indications for therapy with ICIs in different type of cancers. When evaluating patients with hepatotoxicity, it is important to rule out other etiologies before making a diagnosis. Management usually starts with cessation of ICI followed by treatment with corticosteroids and other immunosuppressive therapies. Most patients recover and some are able to resume therapy with ICIs. As more data become available, management strategies may change, and retreatment may become an option for higher grade hepatotoxicity. The main limitation of this review is that, because of a lack of data on the topic, some studies that did not describe the use of RUCAM when assessing for immunotherapy-induced hepatotoxicity were also included. Nonetheless, the conclusions were mainly based on studies that used RUCAM.

Funding

None to declare.

Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Proposed concept for review, collected relevant information, drafted the article, and revised the manuscript with critical revisions (TD), edited the article (GYW), edited the article, critical revision of the article, and final approval of the version to be published (HV).

References

[1] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, *et al*. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020; 382(9):810–821. doi:10.1056/NEJMoa1910549, PMID:32101663.
[2] Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015;13:211. doi:10.1186/s12916-015-0455-8, PMID:26337719.
[3] Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, *et al*. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. Cancer 2018;124(2):271–277. doi:10.1002/cncr.31043, PMID:28960263.
[4] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, *et al*. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372(26):2521–2532. doi:10.1056/NEJMoa1503093, PMID:25891173.
[5] Almutairi AR, McBride A, Slack M, Erstad BL, Abraham I. Potential Immune-Related Adverse Events Associated With Monotherapy and Combination Therapy of Ipilimumab, Nivolumab, and Pembrolizumab for Advanced Melanoma: A Systematic Review and Meta-Analysis. Front Oncol 2020;10:91. doi:10.3389/fonc.2020.00091, PMID:32117745.
[6] Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, *et al*. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4(12):1721–1728. doi:10.1001/jamaoncol.2018.3923, PMID:30242316.
[7] Fu J, Li WZ, McGrath NA, Lai CW, Brar G, Xiang YQ, *et al*. Immune Checkpoint Inhibitor Associated Hepatotoxicity in Primary Liver Cancer Versus Other Cancers: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:650292. doi:10.3389/fonc.2021.650292, PMID:33968750.
[8] Cho YA, Han JM, Kang SY, Kim DC, Youn YJ, Choi KH, *et al*. Analysis of Risk Factors for Hepatotoxicity Induced by Immune Checkpoint Inhibitors. J Immunother 2021;44(1):16–21. doi:10.1097/CJI.0000000000000347, PMID:33290362.
[9] Cheung V, Gupta T, Payne M, Middleton MR, Collier JD, Simmons A, *et al*. Immunotherapy-related hepatitis: real-world experience from a tertiary centre. Frontline Gastroenterol 2019;10(4):364–371. doi:10.1136/flgastro-2018-101146, PMID:31656561.
[10] Gauci ML, Baroudjian B, Zeboulon C, Pages C, Poté N, Roux O, *et al*. Immune-related hepatitis with immunotherapy: Are corticosteroids always needed? J Hepatol 2018;69(2):548–550. doi:10.1016/j.jhep.2018.03.034, PMID:29747956.
[11] Ziemer M, Koukoulioti E, Beyer S, Simon JC, Berg T. Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids. J Hepatol 2017;66(3):657–659. doi:10.1016/j.jhep.2016.11.015, PMID:27908801.
[12] Berraondo P. Mechanisms of action for different checkpoint inhibitors. Hemasphere 2019;3(Suppl):28–30. doi:10.1097/HS9.0000000000000244, PMID:35309798.
[13] Oncology (Cancer) / Hematologic Malignancies Approval Notifications | FDA. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.
[14] Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, *et al*. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18(9):1182–1191. doi:10.1016/S1470-2045(17)30422-9, PMID:28734759.
[15] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, *et al*. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373(1):23–34. doi:10.1056/NEJMoa1504030, PMID:26027431.
[16] Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carceny Costa E, *et al*. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381(21):2020–2031. doi:10.1056/NEJMoa1910231, PMID:31562796.
[17] Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, *et al*. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378(14):1277–1290. doi:10.1056/NEJMoa1712126, PMID:29562145.
[18] Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, *et al*. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. J Clin Oncol 2018;36(14):1428–1439. doi:10.1200/JCO.2017.76.0793, PMID:29584546.
[19] Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, *et al*. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375(19):1856–1867. doi:10.1056/NEJMoa1602252, PMID:27718784.
[20] Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, *et al*. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017; 18(3):312–322. doi:10.1016/S1470-2045(17)30065-7, PMID:28131785.
[21] Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, *et al*. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. J Clin Oncol 2020;38(36):4317–4345. doi:10.1200/JCO.20.02672, PMID:33197225.
[22] Peeraphatdit TB, Wang J, Odenwald MA, Hu S, Hart J, Charlton MR. Hepatotoxicity From Immune Checkpoint Inhibitors: A Systematic Review and Management Recommendation. Hepatology 2020;72(1):315–329. doi:10.1002/hep.31227, PMID:32167613.
[23] Singh S, Hassan D, Aldawsari HM, Molugulu N, Shukla R, Kesharwani P. Immune checkpoint inhibitors: a promising anticancer therapy. Drug Discov Today 2020;25(1):223–229. doi:10.1016/j.drudis.2019.11.003, PMID:31738877.
[24] André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, *et al*. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020;383(23):2207–2218. doi:10.1056/NEJMoa2017699, PMID:33264544.
[25] Lavacchi D, Pellegrini E, Palmieri VE, Doni L, Mela MM, Di Maida F, *et al*. Immune Checkpoint Inhibitors in the Treatment of Renal Cancer: Current State and Future Perspective. Int J Mol Sci 2020;21(13):E4691. doi:10.3390/ijms21134691, PMID:32630154.
[26] Bajwa R, Cheema A, Khan T, Amirpour A, Paul A, Chaughtai S, *et al*. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study. J Clin Med Res 2019;11(4):225–236. doi:10.14740/jocmr3750, PMID:30937112.
[27] Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, *et al*. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med 2006;203(4):883–895. doi:10.1084/jem.20051776, PMID:16606670.
[28] Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, *et al*. Distinct Cellular Mechanisms Underlie Anti-CTLA-4 and Anti-PD-1 Checkpoint Blockade. Cell 2017;170(6):1120–1133.e17. doi:10.1016/j.cell.2017.07.024, PMID:28803728.
[29] Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, *et al*. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 2017;545(7652):60–65. doi:10.1038/nature22079, PMID:28397821.
[30] Yang H, Yao Z, Zhou X, Zhang W, Zhang X, Zhang F. Immune-related adverse events of checkpoint inhibitors: Insights into immunological dysregulation. Clin Immunol 2020;213:108377. doi:10.1016/j.clim.2020.108377, PMID:32135278.
[31] Riveiro-Barciela M, Barreira-Díaz A, Vidal-González J, Muñoz-Couselo E, Martínez-Valle F, Viladomiu L, *et al*. Immune-related hepatitis related to checkpoint inhibitors: Clinical and prognostic factors. Liver Int 2020;40(8):1906–1916. doi:10.1111/liv.14489, PMID:32329119.
[32] Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Available from: https://www.meddra.org/.
[33] Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, *et al*. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 2017;35(7):785–792. doi:10.1200/JCO.2015.66.1389, PMID:28068177.
[34] Jennings JJ, Mandaliya R, Nakshabandi A, Lewis JH. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. Expert Opin Drug Metab Toxicol 2019;15(3):231–244. doi:10.1080/17425255.2019.157474, PMID:30677306.
[35] Tsung I, Dolan R, Lao CD, Fecher L, Riggenbach K, Yeboah-Korang A, *et al*. Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy. Aliment Pharmacol Ther 2019;50(7):800–808. doi:10.1111/apt.15413, PMID:31309615.
[36] Imoto K, Kohjima M, Hioki T, Kurashige T, Kurokawa M, Tashiro S, *et al*. Clinical Features of Liver Injury Induced by Immune Checkpoint Inhibitors in Japanese Patients. Can J Gastroenterol Hepatol 2019;2019:6391712. doi:10.1155/2019/6391712, PMID:31929981.
[37] Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, *et al*. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf 2009;32(1):55–68. doi:10.2165/00002018-200932010-00005, PMID:19132805.
[38] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711–723. doi:10.1056/NEJMoa1003466, PMID:20525992.

[39] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, *et al*. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377(19):1824–1835. doi:10.1056/NEJMoa1709030, PMID:28891423.
[40] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372(21):2018–2028. doi:10.1056/NEJMoa1501824, PMID:25891174.
[41] Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, *et al*. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol 2020;15(3):426–435. doi:10.1016/j.jtho.2019.10.004, PMID:31629915.
[42] Chang CY, Park H, Malone DC, Wang CY, Wilson DL, Yeh YM, *et al*. Immune Checkpoint Inhibitors and Immune-Related Adverse Events in Patients With Advanced Melanoma: A Systematic Review and Network Meta-analysis. JAMA Netw Open 2020;3(3):e201611. doi:10.1001/jamanetworkopen.2020.1611, PMID:32211869.
[43] Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, *et al*. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. J Clin Oncol 2015;33(13):1430–1437. doi:10.1200/JCO.2014.59.0703, PMID:25452452.
[44] Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, *et al*. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet Oncol 2017;18(9):1202–1210. doi:10.1016/S1470-2045(17)30428-X, PMID:28729151.
[45] Boyer M, Şendur MAN, Rodríguez-Abreu D, Park K, Lee DH, Çiçin I, *et al*. Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study. J Clin Oncol 2021;39(21):2327–2338. doi:10.1200/JCO.20.03579, PMID:33513313.
[46] Remash D, Prince DS, McKenzie C, Strasser SI, Kao S, Liu K. Immune checkpoint inhibitor-related hepatotoxicity: A review. World J Gastroenterol 2021;27(32):5376–5391. doi:10.3748/wjg.v27.i32.5376, PMID:34539139.
[47] Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, *et al*. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11(2):155–164. doi:10.1016/S1470-2045(09)70334-1, PMID:20004617.
[48] McGovern BH, Birch C, Zaman MT, Bica I, Stone D, Quirk JR, *et al*. Managing symptomatic drug-induced liver injury in HIV-hepatitis C virus-coinfected patients: a role for interferon. Clin Infect Dis 2007;45(10):1386–1392. doi:10.1086/522174, PMID:17968840.
[49] De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, *et al*. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68(6):1181–1190. doi:10.1016/j.jhep.2018.01.033, PMID:29427729.
[50] Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012;57(8):2233–2240. doi:10.1007/s10620-012-2140-5, PMID:22434096.
[51] Kim KW, Ramaiya NH, Krajewski KM, Jagannathan JP, Tirumani SH, Srivastava A, *et al*. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs 2013;31(4):1071–1077. doi:10.1007/s10637-013-9939-6, PMID:23408334.
[52] Abu-Sbeih H, Wang Y. Hepatobiliary Adverse Events. Adv Exp Med Biol 2020;1244:271–276. doi:10.1007/978-3-030-41008-7_14, PMID:32301021.
[53] Cohen JV, Dougan M, Zubiri L, Reynolds KL, Sullivan RJ, Misdraji J. Liver biopsy findings in patients on immune checkpoint inhibitors. Mod Pathol 2021;34(2):426–437. doi:10.1038/s41379-020-00653-1, PMID:32884128.
[54] Bernardo SG, Moskalenko M, Pan M, Shah S, Sidhu HK, Sicular S, *et al*. Elevated rates of transaminitis during ipilimumab therapy for metastatic melanoma. Melanoma Res 2013;23(1):47–54. doi:10.1097/CMR.0b013e32835c7e68, PMID:23262440.
[55] Sangro B, Chan SL, Meyer T, Reig M, El-Khoueiry A, Galle PR. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320–341. doi:10.1016/j.jhep.2019.10.021, PMID:31954495.
[56] Wang W, Lie P, Guo M, He J. Risk of hepatotoxicity in cancer patients treated with immune checkpoint inhibitors: A systematic review and meta-analysis of published data. Int J Cancer 2017;141(5):1018–1028. doi:10.1002/ijc.30678, PMID:28263392.
[57] Shroff GS, Shroff S, Ahuja J, Truong MT, Vlahos I. Imaging spectrum of adverse events of immune checkpoint inhibitors. Clin Radiol 2021;76(4):262–272. doi:10.1016/j.crad.2020.11.117, PMID:33375984.
[58] Widmann G, Nguyen VA, Plaickner J, Jaschke W. Imaging Features of Toxicities by Immune Checkpoint Inhibitors in Cancer Therapy. Curr Radiol Rep 2016;5(11):59. doi:10.1007/s40134-017-0256-2, PMID:28959504.
[59] Thomas R, Sebastian B, George T, Majeed NF, Akinola T, Laferriere SL, *et al*. A review of the imaging manifestations of immune check point inhibitor toxicities. Clin Imaging 2020;64:70–79. doi:10.1016/j.clinimag.2020.04.007, PMID:32334270.
[60] Nishino M, Hatabu H, Hodi FS. Imaging of Cancer Immunotherapy: Current Approaches and Future Directions. Radiology 2019;290(1):9–22. doi:10.1148/radiol.2018181349, PMID:30457485.
[61] Tirumani SH, Ramaiya NH, Keraliya A, Bailey ND, Ott PA, Hodi FS, *et al*. Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab. Cancer Immunol Res 2015;3(10):1185–1192. doi:10.1158/2326-6066.CIR-15-0102, PMID:26100356.
[62] Zhang D, Hart J, Ding X, Zhang X, Feely M, Yassan L, *et al*. Histologic patterns of liver injury induced by anti-PD-1 therapy. Gastroenterol Rep (Oxf) 2020;8(1):50–55. doi:10.1093/gastro/goz044, PMID:32467761.
[63] Danan G, Teschke R. RUCAM in Drug and Herb Induced Liver Injury: The Update. Int J Mol Sci 2015;17(1):E14. doi:10.3390/ijms17010014, PMID:26712744.
[64] Teschke R, Danan G. Drug induced liver injury with analysis of alternative causes as confounding variables. Br J Clin Pharmacol 2018;84(7):1467–1477. doi:10.1111/bcp.13593, PMID:29607530.
[65] Roberts K, Culleton V, Lwin Z, O'Byrne K, Hughes BG. Immune checkpoint inhibitors: Navigating a new paradigm of treatment toxicities. Asia Pac J Clin Oncol 2017;13(4):277–288. doi:10.1111/ajco.12698, PMID:28699304.
[66] Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, *et al*. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9(6):e002435. doi:10.1136/jitc-2021-002435, PMID:34172516.
[67] Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, *et al*. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv119–iv142. doi:10.1093/annonc/mdx225, PMID:28881921.
[68] Management of immune-related adverse events (irAEs) | eviQ. Available from: https://www.eviq.org.au/clinical-resources/side-effect-and-toxicitymanagement/immunological/1993-management-of-immune-related-adverse-events#collapse150419.
[69] European Association for the Study of the Liver; Clinical Practice Guideline Panel: Chair; Panel members; EASL Governing Board representative. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol 2019;70(6):1222–1261. doi:10.1016/j.jhep.2019.02.014, PMID:30926241.
[70] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al*. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714–1768. doi:10.1200/JCO.2017.77.6385, PMID:29442540.
[71] Cheng R, Cooper A, Kench J, Watson G, Bye W, McNeil C, *et al*. Ipilimumab-induced toxicities and the gastroenterologist. J Gastroenterol Hepatol 2015;30(4):657–666. doi:10.1111/jgh.12888, PMID:25641691.
[72] McGuire HM, Shklovskaya E, Edwards J, Trevillian PR, McCaughan GW, Bertolino P, *et al*. Anti-PD-1-induced high-grade hepatitis associated with corticosteroid-resistant T cells: a case report. Cancer Immunol Immunother 2018;67(4):563–573. doi:10.1007/s00262-017-2107-7, PMID:29289977.
[73] Ahmed T, Pandey R, Shah B, Black J. Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy. BMJ Case Rep 2015;2015:bcr2014208102. doi:10.1136/bcr-2014-208102, PMID:26174726.
[74] Motomura D, Baetz T, Grin A, Flemming JA. Severe Refractory Checkpoint Inhibitor-Related Hepatitis Reversed With Anti-Thymocyte Globulin and n-Acetylcysteine. Hepatology 2020;72(6):2235–2238. doi:10.1002/hep.31396, PMID:32484945.
[75] Chmiel KD, Suan D, Liddle C, Nankivell B, Ibrahim R, Bautista C, *et al*. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011;29(9):e237–e240. doi:10.1200/JCO.2010.32.2206, PMID:21220617.
[76] David S, Hamilton JP. Drug-induced Liver Injury. US Gastroenterol Hepatol Rev 2010;6:73–80. PMID:21874146.