Immune Checkpoint Inhibitors Induced Hepatotoxicity; Gastroenterologists' Perspectives

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ABSTRACT

BACKGROUND:
Immune checkpoint inhibitors (ICIs) have promising clinical activity and are essential medications for patients with several malignancies. However, by deranging the immune system, these novel agents could lead to immune-related adverse events (IRAEs). Hepatotoxicity with checkpoint inhibitors usually results in acute hepatitis or drug-induced liver injury.

METHODS:
This review article discusses the recent clinical evidence available regarding checkpoint inhibitor-induced hepatitis and reviews an approach to their diagnosis and management.

CONCLUSION:
ICIs have improved patients' outcomes with different forms of malignancy; however, ICIs-related liver damage is a clinically significant entity in these patients. All patients should be monitored carefully for IRAEs while undergoing treatment with ICIs.

KEYWORDS:
Liver injury, Checkpoint inhibitors, Immune-related adverse events

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INTRODUCTION

Some of the immunotherapy drugs called immune checkpoint inhibitors (ICIs) are novel and important medications for patients with a number of different malignancies such as breast cancer, renal cell carcinoma, Hodgkin's lymphoma, and hepatocellular carcinoma.[1,2]

These agents are monoclonal antibodies that specifically target down-regulators of the anti-cancer immune responses.[3] Immune checkpoints are a normal part of the immune system, and they protect healthy cells in the body from being attacked and destroyed by a strong immune response.[4] Most ICIs target three key checkpoints: cytotoxic T-lymphocyte associated protein 4 (CTLA-4; ipilimumab, and tremelimumab), programmed cell death receptor 1 (PD-1; pembrolizumab and nivolumab), and programmed death-ligand 1 (PD-L1; atezolizumab, avelumab, and durvalumab).[5] Despite impressive survival benefits and noticeable improvements in disease outcomes following ICI therapy, its use can be associated with serious adverse events related to excessive immune activation.[6] Importantly, immune checkpoint inhibition can stimulate autoreactive T-cells, and this activation can lead to a unique range of toxicities identified as immune-related adverse events (IRAEs).[7] Adverse events include skin rashes, colitis, pancreatitis, nephritis, and hepatitis.[8,9] The gastrointestinal tract appears to be the most commonly affected organ, and IRAEs seem to be characterized by predominant neutrophilic and lymphocytic inflammation.[10] Particularly, the liver is prone to be affected by IRAEs, and the prevalence of ICIs-induced liver injury has been reported to be between 4% and 9% in patients treated with CTLA-4 monoclonal antibodies, and 18% of those treated with a combination of anti-PD-1 and anti-CTLA-4 inhibitors.[11,12] Therefore, addressing hepatic IRAEs has become a significant clinical issue for patients. The primary objectives of this article include reviewing currently available literature regarding ICI-associated acute hepatitis and liver injury while also guiding on novel management and therapeutic interventions that are currently available to manage such complications.

MATERIALs AND METHODS

Medline/PubMed databases were searched thoroughly with search strategies using search keywords "hepatitis", "checkpoint inhibitors", "immune-related adverse events", "Nivolumab" ,"Ipilimumab", "Pembrolizumabto", "Atezolizumab", "Avelumab", "Tremelimumab" and "Durvalumab" to classify studies published between the years 2000 and 2020. All types of related studies, including retrospective, cross-sectional, case reports, and cohorts, were selected. Adults with acute hepatitis or liver injury as a result of checkpoint inhibitor use were included. Studies related to non-humans were excluded from our review. The authors reviewed all selected articles for relevance to checkpoint inhibitor use and hepatotoxicity.

Epidemiology of Hepatotoxicity

Hepatotoxicity with ICIs is relatively common as the major mechanism of action of ICIs involves the infiltration of immune cells into normal and neoplastic tissues.[13,14]

The rate of liver injury with ICIs varies between different checkpoint inhibitors. It has been reported that the incidence of various grades of autoimmune hepatotoxicity with CTLA-4 inhibitors is between 3%-9%,[15-17] however, the hepatotoxicity with PD-1 inhibitors was noted to be between 1%-3%.[18] Additionally, the incidence of hepatotoxicity is much higher with combination therapy, with an incidence rate of 13%–30% for all grades and 6%–19% for ≥ grade 3.[1,19,20] De Martin and colleagues observed acute hepatitis grade ≥3 in 16 patients with an incidence rate of 3.5% when treated with anti-PD-1/PD-L1 and anti-CTLA-4.[21] In a meta-analysis, Wang and colleagues showed that the risk of all and high-grade hepatotoxicity with CTLA-4 inhibitors are higher compared with control regimes. The odds ratio in this study for all-grade hepatotoxicity was 1.24 (95% confidence interval 0.75, 2.05; $P<0.39$) and the odds ratio for high-grade hepatotoxicity (grade ≥3) was 1.93 (95% confidence interval 0.84, 4.44; $P<0.12$). In the same study, the risk of all-grade hepatotoxicity and high-grade hepatotoxicity with the use of PD-1 inhibitors appears to be lower, with the odds ratio for all-grade hepatotoxicity noted to be 1.52 (95% confidence interval 1.24, 1.86; $P<0.0001$) and for high-grade hepatotoxicity was 0.48 (95% confidence interval 0.29, 0.80; $P=0.005$) (Table 1).[22]

Parlati et al demonstrated in a retrospective study that 23.1% of the patients treated with ICIs developed a predominantly cholestatic pattern of liver injury with an incidence of 60.3%, while hepatocellular liver injury and mixed hepatocellular/cholestatic liver injury occurred in 20 (29.4%) and 7 (10.3%) patients, respectively.[36]

Mechanisms of Action

Tumor-associated antigens (TAAs) will be expressed by transformed cells, which can be detected by the patient's immune system.[37] During the process of recognition and subsequent elimination of tumor cells, TAAs will be presented by antigen-presenting cells (APCs) alongside the major histocompatibility complex (MHC) I or II that bind with T-cell receptors (TCRs).[38]

The interactions of TCR with peptide/MHC and CD-28 (stimulatory checkpoint expressed on T cells) with B7 (CD-80) present on APCs lead to variations in gene expression, activation of T cell proliferation, and secretion of cytokines.[39] The CTLA-4 (CD152) and PD-1 (CD279) are two important immune checkpoint receptors, which tumor cells may use as a mechanism

Table 1: Incidence of immune checkpoint inhibitor-related hepatitis in randomized clinical trials

Author	Medication	Hepatitis Incidence %	Total patient	Cancer
Hodi et al[23]	Ipilimumab	3.8	131	Melanoma
Robert et al[24]	Ipilimumab plus dacarbazine	29.1	247	Melanoma
Kwon et al[25]	Ipilimumab plus radiotherapy	1	393	Prostate
Reck et al[26]	Ipilimumab plus paclitaxel and carboplatin	46.6	84	Small cell carcinoma of lung
Tarhini et al[27]	Tremelimumab plus Interferon Alfa-2b	21.6	37	Melanoma
Ribas et al[28]	Tremelimumab	1	325	Melanoma
Borghaei et al[29]	Nivolumab	9	287	Non squamous carcinoma of lung
Topalian et al[30]	Nivolumab	3.7	107	Melanoma
Postow et al[31]	Nivolumab plus ipilimumab	21	94	Melanoma
Hamanishi et al[32]	Nivolumab	40	20	Ovarian
Wolchok et al[33]	Nivolumab plus ipilimumab	53	21	Melanoma
Rosenberg et al[34]	Atezolizumab	3	310	Urothelial
Petrylak et al[35]	Atezolizumab	4	95	Urothelial

of immune resistance against malignant cells.[40] CLTA-4 is a downregulatory of T cell-mediated anti-tumor responses, and it prevents T cell activation and proliferation.[41] Similarly, the interaction between PD-1 and PD-L1/PD-L2 can lead to T cell inactivation.[42]

The mechanisms of IRAEs are not entirely understood; however, some studies are available to further understand the nature of these events. For example, CTLA-4 blockade eliminates CTLA-4-mediated protection from autoimmunity and may lead to serious and life-threatening clinical manifestations that resemble autoimmune conditions involving all organs and tissues, including the hepatobiliary system.[43]Due to activation of T cells, $CD4^+$ helper T cells secrete high levels of cytokines, and $CD8^+$ T cells infiltrate in tissue. Hepatotoxicity from ICI use most often resembles autoimmune hepatitis (AIH), and pathological review of liver biopsy tissue often reveals immune-mediated hepatic injury with focal or confluent necrosis and prominent lymphocytic infiltrate of activated T cells.[9,44,45] Furthermore, ICI-related hepatotoxicity appears to be dose-dependent. Wolchok and colleagues observed no grade 3 to 4 hepatotoxicity with ipilimumab at a dose of 0.3 mg/kg, while ICI-related hepatotoxicity increased to 30% with ipilimumab at a dose of 10 mg/kg in patients treated for advanced melanoma.[46]

Histological Features

Histologically, ICI use can induce various forms of pathological injury to hepatocytes, including panlobular hepatitis, perivenular infiltration with endothelialitis or a cholestatic pattern of injury with bile duct proliferation, as well as mixed portal inflammation with mild lobular necroinflammation.[47,48] In a case series study, Zen and colleagues showed the liver injury was largely characterized by lobular hepatitis with infiltration of $CD3^+$ or $CD8^+$ T cells in seven patients who were treated with nivolumab or ipilimumab. However, they reported that compared with classic AIH, centrilobular zonal necrosis and plasmacytosis were uncommon.[9] While there were some similarities between ICI-induced hepatotoxicity and AIH on review of the liver histology, there were also differences that indicate that ICIs-related liver toxicity might involve a separate idiosyncratic pattern of injury.[45] For instance, in ICIs-related hepatotoxicity, $CD20^+$ or $CD4^+$ lymphocytes are found to be significantly fewer in number, and plasmacytosis and eosinophilic infiltration are less frequently seen in ICIs-related liver injury.[9] Additionally, fibrin ring granulomas have also been reported and considered as pathognomonic for ipilimumab-induced hepatic injury.[49, 50]Moreover, De Martin and colleagues identified two different histological patterns among 16 patients treated with anti- CTLA-4 or anti-PD-1/PD-L1 agents. They reported that granulomatous hepatitis with fibrin deposits was associated more with anti CTLA-4 use, whereas lobular with non-granulomatous hepatitis development is related to anti-PD-1/anti-PD-L1 use (Table 2).[21]

Furthermore, Johncilla et al showed a steatosis pattern similar to non-alcoholic fatty liver disease in 2 of 11 patients with ICIs-induced hepatitis.[31] Given this evidence, it appears that performance of a liver biopsy and pathological evaluation of liver tissue is extremely beneficial in distinguishing between ICIs-induced liver injury, AIH, non-alcoholic fatty liver disease, and drug-induced hepatotoxicity; however additional studies are needed to further evaluate for subtle differences in the patterns of hepatic damage.[44]

Clinical Presentation

The clinical characteristics of ICIs-induced hepatotoxicity are quite heterogeneous but they are usually in line with an autoimmune induced liver injury.[36] Hepatic injury with checkpoint inhibitors typically results in asymptomatic elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and, less frequently, bilirubin. Some patients may have pain in the right upper quadrant, fever, fatigue, or jaundice; however, many patients may also present without symptoms.[12] The *National Cancer Institute* (NCI) and Common Terminology Criteria for Adverse Events (CTCAE) are typically utilized to categorize the severity of immune-related toxicity grading. It is very important to recognize the toxicity grade of immune-related hepatitis as it assists with the treatment options and also provides guidance regarding the optimal time to resume ICI therapy (Table 3).[15]

The median onset of transaminase elevation depends

Table 2: Comparison of the clinicopathologic features of hepatic injury due to ICIs, DILI, and AIH

Feature	ICIs	DILI	AIH
Autoimmune antibody	Absent	ANA, SMA, pANCA	ANA, Anti LKM1, SMA
Histology	PD-1/L1: Lobular, non-granulomatous hepatitis CTLA-4: Central vein endothelialitis, granulomatous hepatitis with fibrin ring deposits[21]	Cholestasis and bile duct injury non-caseating granulomas, mild lobular and portal inflammation[51]	Lymphoplasmacytic interface hepatitis, emperipolesis, and hepatocyte rosettes[52]
Type of immune cells	Eosinophilic infiltration and plasmacytosis less frequently with significantly fewer $CD20^+$ or $CD4^+$ lymphocytes	Prominent intra-acinar lymphocyte Prominent port neutrophils[53]	Prominent intra-acinar plasma cell and eosinophils[53]

Abbreviations: ICI, Immune checkpoint inhibitors; DILI, Drug-induced liver injury; AIH, Autoimmune hepatitis; ANA, Antinuclear antibodies; SMA, Smooth muscle antibodies; pANCA, Perinuclear antineutrophil cytoplasmic antibodies; LKM1, Liver kidney microsomal type 1.

Table 3: Common Terminology Criteria for Adverse Events (CTCAE), version 5[15]

Grading	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hepatitis	AST/ALT<3x ULN and/or total bilirubin < 1.5x ULN	AST/ALT 3-5x ULN and/or total bilirubin 1.5-3x ULN	AST/ALT 5-20x ULN and/or total bilirubin3-10x ULN	Decompensated liver function, AST/ALT>20x ULN and/or total bilirubin >10x ULN	Death

Abbreviations: ULN, Upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

on the type of ICI used and the primary malignancy being treated, but it has been reported that the elevation typically occurs 6-14 weeks following the initiation of the ICI treatment.[54,55] For example, the median onset of hepatitis following nivolumab treatment in lung cancer was reported to be around 25 weeks, but was 4 weeks for melanoma.[56] Hepatitis B virus (HBV) reactivation, which is defined as a reappearance of HBV DNA in patients with previously inactive HBV, is a serious complication in cancer patients who are undergoing immunosuppressive treatment or chemotherapy.[57,58]

ICI Treatment in Chronic Viral Hepatitis

Patients with cancer who have chronic hepatitis B (hepatitis B surface antigen-positive) or hepatitis C (hepatitis C virus RNA positive) infections are always at risk for exacerbation of viral hepatitis in the setting of immunosuppression, and the impact of checkpoint inhibitors on these chronic viral infections is poorly understood.[59] Zhang and colleagues showed that in 114 patients with HBsAg-positive status who were treated with anti-PD-1/PD-L1 agents, the incidence of reactivation of HBV was 5.3%. The inadequacy of prophylactic antiviral therapy was the most significant risk factor, with an odds ratio of 17.50. They recommend screening of all patients for HBV before initiation of anti-PD-1/PD-L1 therapy and initiation of prophylactic antiviral treatment for those who are seropositive (HBsAg positive), regardless of baseline HBV DNA level.[60] Additional considerations regarding HBsAg seroconversion do not appear to be discussed in great detail in the currently available literature; however, they may warrant future investigations in the management of patients with HBsAg positivity receiving ICI treatment.

Conversely, Shah and colleagues noted in a retrospective analysis of patients who were infected with human immunodeficiency virus (HIV), HBV, or HCV treated with ICI therapy that there was no evidence of viral reactivation.[61] Additionally, previous trials proved no cases of HCV-related flares in cancer patients with positive serology for HCV who had undergone treatment with ICIs.[62,63]

Prognosis and Mortality of ICIs-Induced Hepatitis

ICIs-induced hepatitis typically improves after treatment with corticosteroids. The time to resolution is about 8 weeks, and relapses are frequent as corticosteroids are tapered.[64] In the VigiLyza database of 333 anti-PD1/PD-L1 fatalities, 74 deaths (22%) were due to hepatitis. Ipilimumab use in 193 patients resulted in fatality secondary to hepatitis in roughly 16% of the treated patients.[65] Wang and colleagues discovered a fatality rate of 0.04% due to hepatitis among 19,127 patients who were treated with ICIs.[66]

Management of ICIs-Induced Hepatitis

It was recommended to check baseline liver enzymes prior to ICI infusion, followed by monitoring with serial serological surveillance.[67-69] Importantly, despite known ICIs-induced hepatitis, patients should be assessed for other etiologies of hepatitis to exclude viral hepatitis, autoimmune, and drug-related etiologies as well as rhabdomyolysis. Tsung and others showed that of 491 patients treated with pembrolizumab, only a minority of the liver injury cases were related to pembrolizumab-induced hepatotoxicity. The majority of hepatitis was attributed to malignancy-related biliary strictures or cholestasis.[70] Most cases of hepatitis-related to IRAEs may respond well to supportive care and temporary interruption of ICI use.[71] Generally, the management of ICIs-induced liver injury depends on the grade of liver injury.[72] Grade 1 hepatitis can be managed with close monitoring of AST, ALT, and bilirubin levels while the patient continues treatment with the ICI. The ICI should be discontinued if a patient develops grade 2 hepatitis and held until hepatitis improves to a grade 1 level or resolves completely. It is advised to initiate prednisone or an equivalent corticosteroid at 0.5–1 mg/kg/day if the liver enzymes fail to improve or rise upon repeat testing with temporary cessation of the agent. Grade 3 hepatitis or greater can be managed with permanent discontinuation of ICIs, and in those patients who do not respond adequately to corticosteroids and develop worsening hepatitis or progression of their hepatitis to liver injury, the use of an immunosuppressant including azathioprine (1–2 mg/kg), mycophenolate mofetil (500–1,000 mg twice per day), or tacrolimus with serum trough levels targeting 8–10 ng/mL, should be considered (Table 4).[59,69,73]

Discontinuation of ICIs in grade 3 hepatitis might

Table 4: Management algorithms for checkpoint inhibitors hepatitis

ASCO Recommendations[74]	
Grade 1 (G1)	• Continue ICIs with close monitor • Check LFT two times weekly • Supportive care
Grade 2 (G2)	• Hold ICIs temporarily and resume if recover to G1 or less • Start corticosteroid 0.5-1 mg/kg/day prednisone or equivalent if the abnormal LFT elevation persists • Monitoring LFT to every 3 days • May resume ICIs treatment followed by steroid taper over 4 weeks once LFT improves to G1 on corticosteroid 10 mg/day
Grade 3 (G3)	• Discontinue ICIs permanently • Start intravenous corticosteroid 1-2 mg/kg methylprednisolone or equivalent • Start mycophenolate mofetil or azathioprine, If no improvement after 3 days • Daily or every other day LFT • Consider inpatient treatment • Corticosteroid taper around 4-6 weeks once LFT improves
Grade 4 (G4)	• Discontinue ICIs permanently • Administer IV 2 mg/kg/day methylprednisolone equivalents • Start mycophenolate mofetil, If corticosteroid refractory or no improvement after 3 days • Monitor LFT daily • Consider inpatient monitoring • Corticosteroid taper over 4-6 weeks when symptoms improve to G1 or less • Consider transfer to a tertiary care facility with hepatology consult if necessary

Abbreviations: ASCO, American Society of Clinical Oncology; LFT, liver function test; ICIs, Immune checkpoint inhibitors.

be challenging for patients who may benefit strongly from an oncological perspective from ICI therapy, particularly in those patients who may have limited chemotherapeutic options.[74] On the other hand, the safety and benefit of retreatment with ICIs after recovery from an IRAE is unknown.[75] Santini and others showed that 19 out of 39 patients with advanced non-small cell lung cancer who were managed with anti-PD-L1 and their course of treatment was complicated with IRAE, developed recurrent IRAE following administration of ICI therapy. Therefore, they recommended those patients who needed to be admitted in the hospital for an initial IRAE, and those who had already accomplished a complete or partial response before an initial IRAE, not be retreated.[76] Based on which ICI was used, the response of the primary malignant cells to the ICI, and the response of liver enzymes following ICI discontinuation, the physician would be able to weigh the risks versus benefits of restarting ICI therapy.[77] Other treatments for ICIs-induced hepatitis have been explored. For example, the tumor necrosis factor-alpha (TNF-α) blocker infliximab is not recommended for the treatment of ICIs-induced hepatitis, given the concern of liver toxicity.[69] Additionally, Chmiel and colleagues reported a case of severe steroid-resistant fulminant hepatitis induced by ipilimumab that resolved with anti-thymocyte globulin. They showed that the elevation of hepatic transaminases improved significantly within 24 hours after 1.5 mg/kg of anti-thymocyte globulin for 2 consecutive days.[78]

Riveiro-Barciela et al described the effective use of plasma exchange (PE) (1500 mL of 5% albumin plus four units of plasma as replacement fluid) to treat fulminant hepatitis related to ipilimumab use in patients with melanoma. They showed that PE could help to remove ipilimumab since this molecule had some ideal target characteristics, such as a low volume of distribution (0.1 L/kg) and high molecular weight (148 000 Da).[79]

CONCLUSION

ICIs have improved patients' outcomes with different forms of malignancy; however, ICIs-related liver damage is a clinically significant entity in these groups of patients.[80] All patients should be monitored carefully for IRAEs while they are undergoing treatment with ICIs. Prompt recognition of hepatitis is important to ensure that proper treatment is started promptly. The incidence of hepatotoxicity depends on the type and dosage of agents and appears to be more severe with CTLA-4 and PD-1 combination therapy. Management of severe ICIs-related hepatitis should consist of termination of the ICI and treatment with corticosteroids. The management should be escalated to other immunosuppressive agents for those patients who do not demonstrate a significant response to corticosteroids. Patients with severe or corticosteroid-refractory hepatitis will benefit from collaboration between hepatology and oncology care teams to determine appropriate courses of action on an individualized basis for each patient.

In summary, the rates of ICIs-induced hepatitis, according to several trials are appeared to be less frequent compared with the most common IRAEs; however, physicians need to uphold a low threshold for evaluation and treating suspected immune hepatitis as delays can lead to permanent discontinuation of cancer therapy.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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