Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

Management of autoimmune and viral hepatitis in immunotherapy: a narrative review※

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Background and Objective: Cancer immunotherapy has firmly established itself as a pillar of cancer care due to its advantages over traditional anti-tumor therapy but also carries limitations due to potential for severe adverse reactions. This review highlights the current understanding and management of patients with autoimmune and viral hepatitis immune in the setting of immune checkpoint inhibitor (ICI) therapy.

Methods: A literature search was conducted on PubMed, Scopus, Google Scholar SEER*Stat databases (from inception to December 2022) using search terms: "immune checkpoint inhibitor", "autoimmune hepatitis", "viral hepatitis", "HBV pathogenesis", "HCV pathogenesis", "HBV reactivation", "HCV reactivation", "cancer immunotherapy", "immune related adverse events", "immune related hepatitis".

Key Content and Findings: Pre-existing autoimmune disease (AD), whether active or inactive, can predispose patients receiving ICI therapy to develop autoimmune disease flares or immune-related adverse events (irAEs). Thus, patients with AD have routinely been excluded from clinical trials and data on safety of ICI therapy are limited. Hepatic irAE can be seen in ICI therapy and is a distinct entity from autoimmune hepatitis (AIH). ICI therapy alters the immune environment in patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Patients who had prior exposure to HBV are at risk for viral reactivation. However, the prevalence of viral hepatitis in patients receiving immunotherapy is under-recognized and can lead to increases in liver biochemical tests as well as deterioration of liver function ultimately limiting treatment.

Conclusions: The high morbidity and mortality associated with immune-related hepatitis emphasizes the need for screening of underlying diseases, including autoimmune and viral hepatitis, prior to initiation of ICI. Presence of AIH or chronic viral hepatitis is the most important risk factor for hepatic adverse events in ICI therapy. Screening for AIH, HBV and HCV is paramount in patients who will undergo ICI therapy.

Keywords: Autoimmune hepatitis (AIH); hepatitis B virus (HBV); hepatitis C virus (HCV); immunotherapy; immune checkpoint inhibitors (ICIs)

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※ Special series on Comprehensive Care for Patients with Hepatocellular Carcinoma: Insights from the 2022 San Antonio Liver Cancer Symposium.

Introduction

Background

The understanding of immune surveillance, by which innate immune cells eliminate cancer cells, has provided novel therapeutic options for patients with otherwise advanced and devastating cancers. Cancer immunoediting highlights the juxtaposed role of the immune system protecting against tumor growth while also shaping tumor immunogenicity (1). Tumor immunotherapy, modulates the native immune system to attack multiple targets in cancer cells (2). Emerging immunotherapies show promising efficacy in treating not only malignancies but also autoimmune, infectious, and allogenic transplant-related diseases (3).

Alteration of the immune microenvironment can unfortunately result in tissue toxicity, presenting as both acute and chronic immune-related adverse events (irAEs) thereby limiting its clinical use (4).

Rationale and knowledge gap

Liver-related injuries, including immune checkpoint inhibitor (ICI)-mediated hepatitis, are estimated to affect up to 22% of patients receiving immunotherapy (5). Also of concern, is the risk of exacerbating liver injury in patients with autoimmune liver disease or patients infected with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV), as immunotherapy can damage liver function due to the immune response against viral antigens (6,7). With the increasing use of ICI, a more thorough screening and manement of liver disease is imperative to ensure successful outcomes. However, current data and guidelines remain limited.

Objective

In this review article, we highlight the current understanding and management of autoimmune and viral hepatitis in cancer immunotherapy with a strong focus on ICIs. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-250/rc).

Methods

The authors conducted an independent literature search and review utilizing several databases and search terms (*Table 1*).

Immunotherapy and autoimmunity

ICIs

Tumor immunotherapy encompasses an expansive group of treatments categorized based on their immune system targets which include immune checkpoints, tumor-infiltrating lymphocyte (TIL) transfer, engineered T cell receptors, chimeric antigen receptor (CAR) T cells, regulatory T cells (Treg), and natural killer (NK) cells (3). Among these immunotherapies, ICI therapy has become an immutable mainstay in the treatment of cancer. Immune checkpoints are molecules that regulate immune responses and are often utilized by tumor cells to evade immunosurveillance (8). Blockade of immune checkpoints augments anti-tumor activity by enhancement of native immune response (9). ICIs including cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand programmed death-ligand 1 (PD-L1), and lymphocyte-activation gene 3 (LAG-3) activate the immune system, disinhibit T-cell antitumor function, and eliminate tumor cells (10,11) (*Figure 1*). CTLA-4 inhibits T-cell activation by the downregulation of co-stimulatory ligands CD80 and CD86 (12). Anti-CTLA-4 agents promote T-cell activation and have been shown to induce immune response both *in vivo* and *in vitro* to cause tumor regression (13,14). The co-inhibitor receptor PD-1 is activated by PD-L1 and PD-L2, resulting in suppression of T-cell receptor (TCR)-mediated lymphocyte proliferation and cytokine release (15). Increased PD-L1 and PD-L2 gene expression is seen in malignant tissue (9) and is associated with poor disease prognosis in cancer types including renal cell carcinoma (16,17), esophageal cancer (18), urothelial cancer (19) and pancreatic cancer (20). Blockade of this pathway is shown to potentiate the cytotoxic ability of T cells against malignant cells (21). Combination monoclonal antibodies of co-expressed molecules PD-1/LAG-3 are approved for use in advanced melanoma, and have been promising in the management of lung, colorectal, and liver cancer (22). Blockade of this pathway potentiates the cytotoxic ability of T cells against malignant cells (21).

The first ICI agent, Ipilimumab (Bristol-Myers Squibb) was approved in 2011 for the treatment of metastatic melanoma. In an open-label three phase trial of 676 patients with unresectable Stage III or IV metastatic melanoma, Ipilimumab provided greater median overall survival compared to active control [10.0 *vs.* 6.4 months; hazard ratio (HR) 0.68; P<0.001] (23). Severe irAEs occurred in 10–15% of patients. Pembrolizumab (Merck Sharp & Dohme

Table 1 Search strategy summary

Items	Specifications
Date of search	October 5, 2022–February 19, 2023
Databases and other sources searched	PubMed, Scopus, Google Scholar, American Association for the Study of Liver Diseases guidelines, SEER*Stat databases
Search terms used	"Immune checkpoint inhibitor", "autoimmune hepatitis", "viral hepatitis", "HBV pathogenesis", "HCV pathogenesis", "HBV reactivation", "HCV reactivation", "cancer immunotherapy", "immune related adverse events", "immune related hepatitis"
Timeframe	Studies published prior to 2023
Inclusion criteria	Restricted to English language data, including but not limited to randomized control trials, meta-analysis, systematic reviews, clinical practice guidelines, and case series
Selection process	Authors independently performed literature review and selection

HBV, hepatitis B virus, HCV, hepatitis C virus.

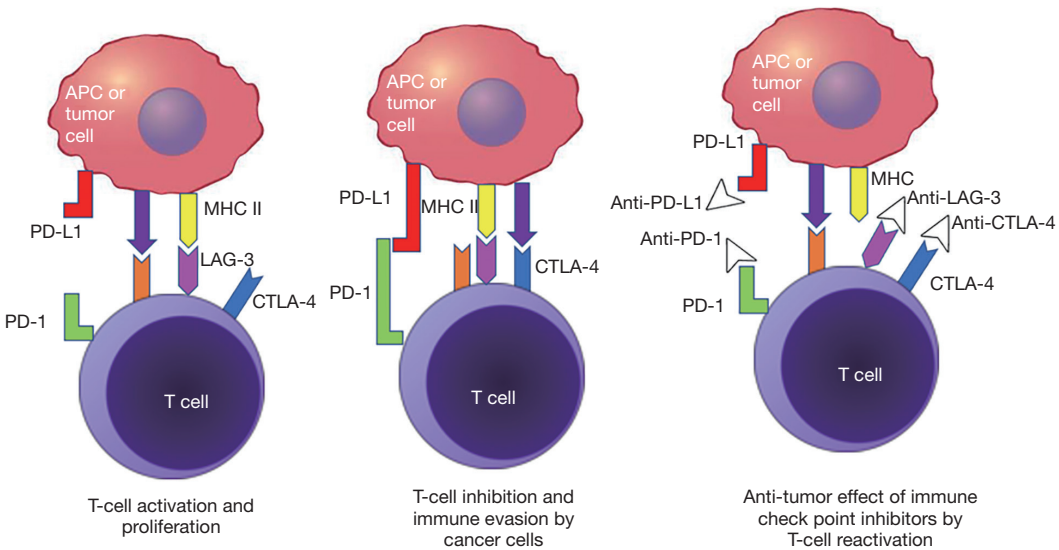

Figure 1 Immune checkpoint inhibition. APC, antigen presenting cell; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; MHC, major histocompatibility complex; LAG-3, lymphocyte activation gene 3; CTLA-4, cytotoxic T cell antigen 4.

Corp.) was compared against ipilumumab for the treatment of melanoma and demonstrated improvement in survival hazard ratio of 0.63 (95% CI: 0.47–0.83, P<0.001) thus in 2014 was the first anti-PD-1 granted accelerated approval for treatment of unresectable metastatic melanoma (24). Subsequently, several ICIs have been approved, several of which are approved as first line therapy in solid organ cancers (*Figure 2*).

Limitations to ICI therapy include inefficacy due to resistance and intolerance due to adverse effects. Primary resistance can occur in the setting of ICI gene expression on tumor cells whereas secondary (acquired) resistance occurs by loss of function mutations in interferon (IFN) response or inadvertent upregulation of alternative immune checkpoints (4,9). Adverse events may range from mild tissue impairment to fatal toxicities, and have been shown to affect a wide range of organ systems including the liver, colon, lungs, pituitary, thyroid, skin, and less commonly, the heart and nervous system (25).

Immune-related adverse events

ICI mediated adverse events and toxicity have been extensively reported. Toxicities from ICIs can be divided

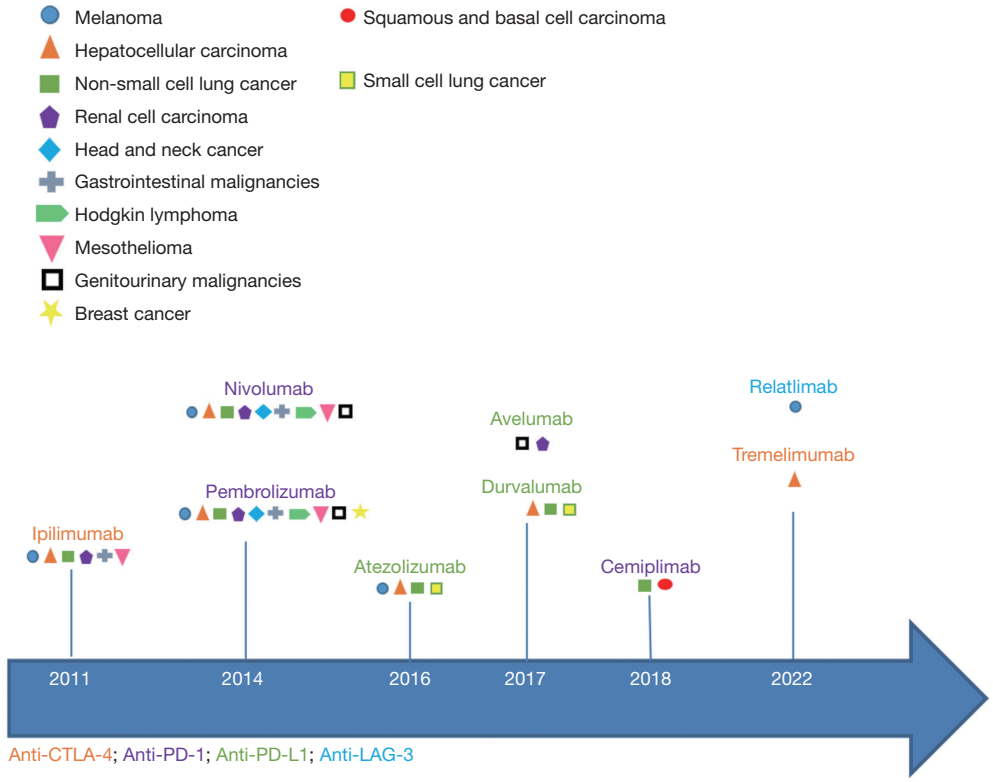

Figure 2 FDA-approved immune check point inhibitors. CTLA-4, cytotoxic T cell antigen 4; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; LAG-3, lymphocyte activation gene 3; FDA, Food and Drug Administration.

Table 2 CTCAE terminology criteria for adverse events

Grades	Symptoms	Intervention
Grade 1	Mild, asymptomatic or mild symptoms	Clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; liming age-appropriate instrumental activities of daily living	Minimal, local or noninvasive intervention
Grade 3	Severe or medically significant but not immediately life threatening; disabling; liming	Hospitalization or prolongation of hospitalization indicated
Grade 4	Life threatening consequences	Urgent intervention indicated
Grade 5	Death related to adverse events	

CTCAE, Common Terminology Criteria for Adverse Events.

into irAEs or adverse events of special interest (AEoSI), and infrequently, infusion-related reactions (26). ICIs activate T cells, thus, irAEs are thought of as autoimmune side effects of immunotherapy (27). IrAEs typically occur within the first three months of ICI initiation, but have also been documented to occur up to a year after initiation (13,26,28). Toxicity is graded on the Common Terminology Criteria for Adverse Events (CTCAE) scale with grade 5 representing death (*Table 2*) (29). The use of anti-CTLA-4 agents is associated with overall and high-grade irAEs, 74% (95% CI: 65–79%), and 24% (95% CI: 18–30%), respectively (30). The incidence of overall and high-grade irAEs with use of anti-PD-1/PD-L1 is 74% (95% CI: 69–79%) and 14% (95% CI: 12–14%), respectively (31). Combination therapy with both agents is associated with the highest incidence of overall and high-grade irAEs, 88% (95% CI: 84–92%) and

Table 3 Hepatitis grading scale and proposed management of ILICI

Injury	Symptoms	Liver enzymes	Management strategy
Grade 1	Asymptomatic	AST/ALT >3× ULN and/or Bilirubin >ULN – 1.5× ULN	Continue ICI therapy and recheck enzymes in 1 week
Grade 2	Asymptomatic	AST/ALT >3–5× ULN	Hold ICI and start oral prednisolone 1 mg/kg
Grade 3	Symptomatic liver dysfunction +/– enzymes or compensated cirrhosis	AST/ALT >5–20× ULN and/or bilirubin 3–10× ULN or fibrosis by biopsy	Discontinue ICI; start oral prednisolone 1 mg/kg or IV methylprednisolone 2 mg/kg based on degree of elevation
Grade 4	Decompensated liver function	AST/ALT >20× ULN and/or bilirubin >10× ULN	Permanently discontinue ICI start IV methylprednisolone 2 mg/kg; consider hepatology consult and liver biopsy

ILICI, immune-mediated liver injury caused by immune checkpoint inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; ICI, immune checkpoint inhibitor; IV, intravenous.

41% (95% CI: 35–47%), respectively (31). The presence of irAEs does not adversely affect overall survival.

Various irAEs have been described including pruritis, rash, colitis, liver toxicity, endocrinopathies (e.g., hypothyroidism, new onset type 1 diabetes), hypophysitis, pneumonitis and arthralgias (32). Hypothyroidism and pneumonitis are more commonly seen in patients treated with anti-PD-L1 agents, whereas rash, colitis and hypophysitis are commonly seen in those treated with anti-CTLA-4 agents. Hepatitis, colitis and pancreatitis are among the more clinically severe irAEs (grade 3 or 4) requiring discontinuation of ICIs (33,34). Rarer toxicities include but are not limited to interstitial nephritis, pancreatitis, myocarditis, myositis, arthritis, and ocular toxicities (34).

Hepatic irAEs carry an incidence of 5–10% in single-agent ICI therapy (26). ICI hepatitis, now referred to as immune-mediated liver injury caused by ICI (ILICI) differs based on the type of immunotherapy, dose, and the existence of pre-exisiting liver conditions. Hepatitis, defined as serum elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), is graded based on degree of elevation: mild/grade 1, moderate/grade 2, severe/grade 3 and life threatening/grade 4 (*Table 3*) (35). However, there can be a heterogenous pattern of injury, encompassing hepatocellular, cholestatic, or both (36). Onset of ILICI is typically around 6–12 weeks after initiation of therapy (29). Anti-PD-L1 therapy can lead to a prolonged course of ILICI compared to anti-CTLA-4 agents, 8–9 *vs.* 3 weeks, respectively (37-39). ILICI typically resolves in 4–6 weeks (40).

Occurrence of ILICI was initially reassuring. The phase 2 study of ipilimumab for advanced melanoma reported only 3% ≥ grade 3 liver adverse events and complete resolution of all liver-related AE (41). In a multicenter study of 146 patients treated with ICI, 46.3% developed hepatitis were asymptomatic at presentation, though 45.73% developed hepatitis categorized as severe (42). However, this contrasts with reports of greater burden of hepatic irAEs in real-world settings, including cases of acute liver failure (43-45). In a meta-analysis of fatal toxic effects of ICIs, hepatitis caused 22% of deaths (25). ILICI is higher in patients receiving combination therapy , with a reported incidence of 25–30%, than those on monotherapy, with a reported incidence is 5–10% (5,28,46-48).

The incidence of hepatic irAEs is greater in patients treated for primary liver cancers, likely due to the presence of underlying liver disease. In the initial trial, Checkmate 040, evaluating nivolumab (Bristol-Myers Squibb, 2014) in patients with advanced hepatocellular carcinoma (HCC), incidence of ≥ grade 3 ALT elevation was 8% (49) compared to 0% in trials for lung cancer (50-52) and 0–4% in trials for melanoma (5,28,53). A review of clinical trials found that patients with HCC treated with ICI have substantial increases in AST/ALT, though severity did not lead to any interruption of therapy (54). In the KEYNOTE-224 trial evaluating pembrolizumab (Merck, 2016) in patients with HCC, 9% of patients developed ALT elevations of any grade, with 4% of patients with ALT elevation ≥ grade 3 (55). Use of tremelimumab (AstraZeneca, 2022), an anti-CTLA-4 antibody, and tumor ablation for the treatment of HCC was associated with ALT elevations of any grade ≥ grade 3 in 19% and 9% of patients, respectively (56). Nivolumab and ipilimumab combination therapy for the treatment of HCC led to a rise in ALT levels of any grade and ≥ grade 3 in 8–16% and 0–8% of patients, respectively (57). In those receiving the combination of tremelimumab and durvalumab (AstraZeneca,

Table 4 Summary of hepatotoxicity from ICI treatment for HCC

Immunotherapeutic agent (study)	AST or ALT ↑	Liver failure	Autoimmune hepatitis or immune-mediated hepatitis	HBV or HCV virologic breakthrough
Nivolumab (CHECKMATE 459)	+	+	+	Not evaluated
Nivolumab + ipilimumab (CHECKMATE 040)*	+	None	+	+
Pembrolizumab (KEYNOTE 224)	+	+	+	Not evaluated
Tremelimumab + durvalumab (HIMALAYA)	+	+	+	Not evaluated
Atezolizumab + bevacizumab (IMbrave 50)	+	+	+	Not evaluated
Lenvatinib + pembrolizumab (KEYNOTE 524)	+	+	+	Not evaluated

↑, increase; +, present; *, study ongoing. ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

2017), elevated ALT levels of any grade and ≥ grade 3 were seen in 20% and 5% of patients, respectively (58). The current first line treatment for unresectable HCC is the combination of an anti-PD-L1, atezolizumab (Genentech, 2016), with a vascular endothelial growth factor, bevacizumab (59) based on favorable results from the IMbrave 150 trial which did not demonstrate any increased liver toxicity; ALT elevations of all grades and ≥ grade 3 were seen in 14% and 3.6% of patients, respectively (60). In patients who are undergoing treatment for HCC with ICI agents, it is imperitive that any underlying liver disease is evaluated and adequately managed prior to initiation of ICI treatment given hepatotoxicity concerns (*Table 4*).

ILICI vs. AIH

While ILICI shares several traits with AIH, they are distinct entities with differing clinicopathological features. Determination of ILICI requires an assessment to exclude other causes such as autoimmune or viral hepatitis. Clinical features of ILICI include systemic symptoms with a rise in aminotransferases. Antinuclear antibodies or IgG elevations are not seen (61). Imaging findings are nonspecific and include hepatomegaly, peri-portal edema, and lymphadenopathy (62) while histological assessment often reveals acute hepatitis with a panlobular distribution of lymphocytic infiltrate with patchy or confluent areas of necrosis, as seen in cases of AIH, viral hepatitis or drug-induced liver injury (63). Pathological changes include presence of histiocytic sinusoidal infiltrates, microgranulomas, and central vein endotheliitis but with the notable absence of a consistent plasma cell predominant infiltrate (64). Histological features may differ between anti-CTLA-4 and anti-PD-1/PD-L1 hepatitis in which granulomatous hepatitis with fibrin-ring granulomas and central vein endotheliitis may be seen in the former and lobular hepatitis can be present in the latter (65). Additionally, immunostaining will reveal increased presence of CD3+ and CD8+ cytotoxic lymphocytes and fewer CD20+ B cells and CD4+ T cells (61,66). A summary of the differences between ILICI and AIH are described in *Table 5*.

Initial management of ILICI includes pausing immunotherapy. Guidelines for the Society for Immunotherapy of Cancer (SITC), the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) recommend treatment with corticosteroids with doses in proportion to grade of hepatitis, up to 2 mg/kg/day (40,51,67). However, liver test findings may dramatically improve with just cessation of immunotherapy alone, without the addition of corticosteroids (36,68). There are several proposed management protocols for patients who develop severe liver toxicity due to ICI use (*Table 3*) (36,68,69). Challenges in managing ICI toxicity include late recognition, inadequate workup, and delayed treatment (69).

In a prospective, multicenter, noninterventional study of patients who developed ≥ grade 3 ILICI, 87% received single agent ICI therapy, among which 75% developed cases of severe irH (39). This cohort of patients were then compared to patients with AIH, who were younger on average (55 *vs.* 66 years). The AIH group had higher prevalence of cirrhosis (16% *vs.* 0%, P=0.008) and higher Model For End-Stage Liver Disease (MELD) score (15 *vs.* 8, P=0.11) than the irH group. An ANA titer >1:80 was seen in 84% of AIH compared to 25% of irH. Patients with AIH had higher median IgG values of 1,706 *vs.* 916 mg/dL

Table 5 Comparison of ILICI and AIH

Characteristics	ILICI	AIH
Clinical features	• Older age	• Younger age
	• No gender prevalence	• Female predominant
	• Symptoms range from asymptomatic to rare cases of acute liver failure	• Symptoms range from asymptomatic to acute liver failure
	• Lack of other autoimmune diseases	• Presence of other autoimmune diseases
Laboratory features	• ↑ AST, ALT, ALP/GGT	• ↑ AST, ALT, IgG
	• Negative ANA (elevated 50%) and normal IgG	• ↑ ALP/GGT, bilirubin (possibly)
		• + ANA (high titer), ASMA, anti-LKM1 (possibly)
Histopathology	• Granulomas	• Plasmacytosis
	• $CD8^+$	• $CD4^+/CD20^+$
Treatment	• Steroids may not always be required	• Steroids required
	• Short courses, high dose	• Other immunosuppressant agents may be required
Recurrence risk	• Rare	• High

↑, increase; +, present. ILICI, immune mediated liver injury caused by immune check point inhibitors; AIH, autoimmune hepatitis; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; IgG, immunoglobulin gamma; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; anti-LKM1, anti-liver kidney microsomal antibody-1.

(P<0.001). Also, irH patients required treatment of higher corticosteroid dose (median of 60 *vs.* 30 mg) initially and for a shorter duration of therapy (2.3 *vs.* 7 months) compared to the AIH patients. The AIH group also required the use of a second immunosuppressive drug in 97% of patients compared to 42% in the irH group (39).

Autoimmune disease

Patients with underlying autoimmune disease were excluded from trials due to concern for susceptibility for irAEs. Real-world data has supported this theory. In a prospective study including 45 patients with 53 pre-existing autoimmune disease (AD) treated with anti-PD-1 antibody for mainly melanoma and non-small cell lung cancer, irAEs occurred in 44% of patients with preexisting ADs (versus in 29% AD-free) and irAE-free survival time was significantly shorter in preexisting AD patients than AD-free patients (median: 5.4 *vs.* 13 months, P=0.0002) (70). In this study, the overall survival time and objective response rates, however, did not differ significantly between preexisting AD and AD-free groups (P=0.38 and 0.098, respectively) (70). In a multicenter, retrospective observational study of 751 patients with melanoma and non-small cell lung cancer treated with anti-PD-1 agents, 11% of which had preexisting AD (82% with inactive disease and 18% with active disease), the all-grade incidence of irAEs was 65.9% in patients with preexisting ADs compared to 39.9% in those without (P<0.001) (71). In this study, 47% of patients developed a flare of their underlying autoimmune disease (71).

Exacerbation of underlying autoimmune disease while receiving ICI treatment is a validated concern. In the largest series of 41 patients with preexisting AD and treatment with ipilimumab, 29% experienced flare of their preexisting disease while 29% developed additional irAEs (72). In a systematic review of 49 studies evaluating preexisting autoimmune disease in the setting of ICI use, 92 of 123 patients (75%) had exacerbations of ADs (41%), development of irAEs (25%), or both (11%) (73). Overall, there was no significant difference in frequency of disease flare or irAEs seen between patients with active or inactive disease (67% *vs.* 75%) (73). A study of 112 patients with preexisting AD reported AD flares and/or irAEs in 71% of patients of which 43% required immunosuppressive therapy and 21% required discontinuation of the agent (74). Patients who were already on immunosuppressive therapy at baseline had worse outcomes with shorter median progression-free survival when compared to those not on

Table 6 Diagnosis of autoimmune hepatitis

Features	Criteria
Clinical	• Exclusion of viral, hereditary, metabolic, cholestatic, and drug-induced diseases
Laboratory	• ↑ AST, ALT
	• ↑ Serum IgG levels
Autoantibodies	• + ANA
	• + ASMA
	• + Anti-LKM1
Histopathology*	• Interface hepatitis
	• Plasma cell infiltration
	• Lobular hepatitis

↑, increase; +, positive; *, histopathological diagnosis must be present along with one of the other (clinical, laboratory or serological markers) features as supporting evidence to make a diagnosis of autoimmune hepatitis. AST, aspartate aminotransferase; ALT, alanine transaminase; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; Anti-LKM1, anti-liver kidney microsomal antibody-1; IgG, immunoglobulin gamma.

baseline immunosuppressive therapy (3.8 *vs.* 12 months; P=0.006) (74). Exacerbation of AD and development of irAEs were deemed to be manageable in these studies. More recently, a multicenter retrospective study of 123 patients with preexisting ADs treated with ICIs demonstrated exacerbation of underlying AD, development of irAE, or both in 25%, 35% and 10% of patients, respectively (75). Of these, grade 4 exacerbation and fatal toxicity were observed in 9% of patients. There was no no significant difference observed between those receiving anti-CTLA4 agents or anti-PDL1 agents (57.1% *vs.* 60.3%, respectively; Fisher's P>0.999) (75). Use of immunotherapy and its expected efficacy must be balanced against potential toxicity issues in patients with underlying autoimmune disease since there is risk of severe flare.

The concern for flare of autoimmune disease also extends to patients with autoimmune liver disease despite the lack of present data. Patients with autoimmune liver disease were not included in studies, but the concern is risk of not only a flare in underlying autoimmune hepatitis (AIH) but additional ICI mediated liver toxicity. Testing and screening for AIH prior to initiating ICI therapy is prudent, especially in patients with other concurrent ADs (67). AIH lacks a signature diagnostic marker thus diagnosis is based on characteristic clinical and laboratory findings along with histological abnormalities (*Table 6*) (76). First-line treatments including prednisone and azathioprine control hepatic inflammation and achieve biochemical remission with an ideal laboratory response as normalization of serum ALT, AST and IgG levels (77). Presence of AIH itself should not be a contraindication to treatment with ICI, although close monitoring and follow-up are essential to monitor for AD flare and *de novo* irAEs. More longitudinal studies are needed to assess definitive effects of ICIs in patients with autoimmune liver disease.

Immunotherapy and viral hepatitis

HBV infection is a global health concern affecting approximately two billion people worldwide (78). An estimated 71 million people worldwide are living with chronic hepatitis C (79). Active and persistent viral infection is associated with hepatic disease progression and risk of development of HCC. Management of hepatitis B and C infection in the setting of immunotherapy hinges upon understanding differences in pathogenesis.

HBV pathogenesis

The HBV is an enveloped circular and partially double-stranded Hepadnaviridae DNA virus that infects hepatocytes (80). The stages of HBV infection are hallmarked by various genes corresponding with infection activity: S gene encoding hepatitis B surface antigen (HBsAg), C gene encoding pre-genomic RNA which forms the hepatitis B core antigen (HBcAg), and a precore protein derivative that encodes the hepatitis B e antigen (HBeAg) (*Figure 3*) (81). In contrast to other hepatic viruses, HBV DNA embeds into the host hepatocyte genome and converts into a covalently closed circular DNA (cccDNA) that is stabilized in the hepatocyte allowing it to persist in a latent state (82). A complete cure of HBV infection is defined by HBV cccDNA eradication, rendering viral replication impossible (83).

In an acute infection, HBV spreads quickly and effectively throughout hepatic parenchyma due to the highly vascular nature of hepatic tissue and ability to evade detection by innate immunity (84). Clearance of HBV infection is via the adaptive immune system and thought to be dependent on $CD8^+$ T cell response, which can be negated by poor CD4 T cell function via weak IFN-γ activation (85). The majority of immunocompetent adults who develop HBV infection by horizontal transmission are able to successfully clear infection, with less than 10% of these cases becoming chronic

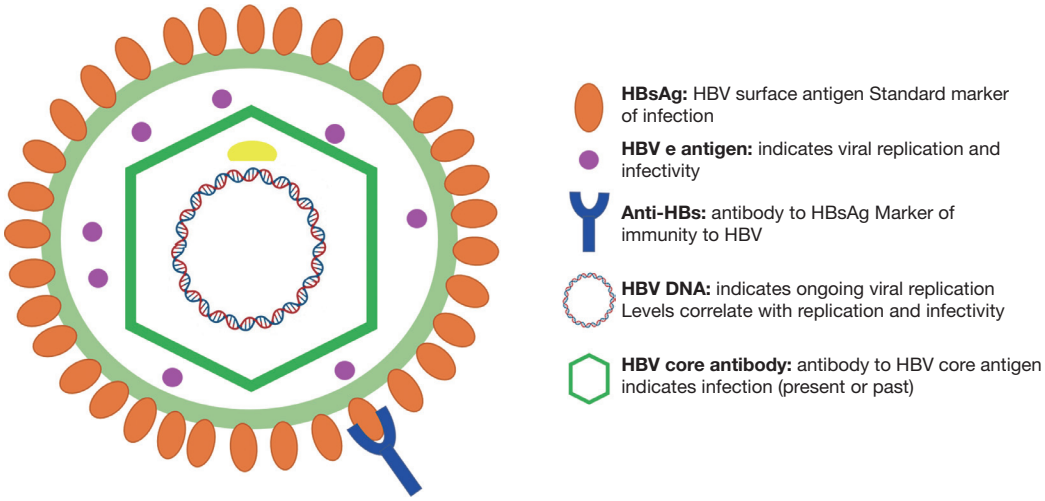

Figure 3 Serologic markers in hepatitis B infection. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Anti-HBs, anti-hepatitis B surface antibodies.

Table 7 Phases of chronic HBV infection

Phase of chronic infection	HBV load	HBeAg	ALT level	Histological inflammation or fibrosis
Immune tolerant	+++	+	Normal	None to minimal
Immune active	++	+	Elevated	Moderate to severe
Chronic inactive	–	–	Normal	Absent with variable fibrosis
Chronic immune-reactivation HBV	+	–	Variable	Variably present

+, positive; –, negative. HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; ALT, alanine transaminase.

HBV. Alternatively, vertical transmission of HBV becomes chronic in more than 90% of cases due to HBV precore protein (HBeAg) that crosses the placenta and facilitates viral persistence by inhibiting induction of the T cell response and creating immune tolerance (86).

Chronic HBV infection is differentiated into 4 phases based on HBV DNA level, ALT level, HBeAg positivity and liver histology (*Table* 7) (81,87). The prolonged, continuous exposure to high levels of viral antigen results in exhaustion of HBV-specific CD8+ T cell activity causing impairment of multiple immune processes (84,88). Active liver injury is only avoided if HBV replication remains inhibited by antiviral therapy (89). In the chronic inactive state, a reservoir of stable circular HBV DNA and its viral proteins exist in hepatocytes while serum HBV DNA remains undetectable (90).

Hepatitis B reactivation

Complete eradication of cccDNA has not been achieved with either the host immune response or antiviral treatment with nucleos(t)ide analogues. The presence of cccDNA allows for HBV reactivation (HBVr) when there is significant disturbance in the balanced state between viral replication and the host immune system. This can occur sponataneously or in response to therapeutic agents that affect the host immune system and immune microenvironment (91). Various definitions have been proposed, but the updated guideline by the American Association for the Study of Liver Diseases (AASLD) defines HBVr when any of the following criteria are fulfilled: (I) a ≥2 log (100-fold) increase in HBV DNA compared to the baseline level; (II) HBV DNA ≥3 log(1,000) IU/mL in a patient with previously undetectable level; or (III) HBV DNA ≥4 log(10,000) IU/mL if the baseline level was not available (87).

Various factors affect reactivation of HBV including HBsAg positivity, HBeAg positivity and higher HBV DNA levels (>10,000 IU/mL) (92,93). Clinical presentation

of HBVr ranges from silent without overt hepatitis to fulminant liver failure (93). HBVr is associated with multiple different treatments including ICIs, tumor necrosis factor-a inhibitors, immunosuppression by corticosteroids, systemic chemotherapy, biologic antibodies such as anti-CD20 like rituximab or anti-tumor necrosis factor-α like infliximab, and even locoregional hepatic interventions such as transarterial chemoembolization (TACE) to treat HCC (94).

HBV seropositivity was evaluated for predisposition for HBVr in a historical cohort study which found reactivation occurred in 1% of HBsAg positive patients (5 of 511) compared with 0% of HBsAg negative patients (0 of 2,954) (95). Patients receiving antiviral prophylaxis had 0.4% reactivation rate compared to 6.4% in those without prophylaxis (57).

HCV pathogenesis

HCV is an enveloped RNA Hepacivirus with significant heterogeneity, thus its pathogenesis is not completely understood (96). Initial response to infection is via innate immunity (96). Over time, HCV has mutated and evolved to evade this detection, further contributing to the high rate of conversion to chronic HCV infection (96). Adaptive immunity-mediated elimination of HCV relies on helper T cell response. Sustained immune response is often insufficient in clearing HCV; most patients develop chronic HCV infection, with 74–86% of patients developing persistent viremia (97).

Persistent HCV replication in chronic infection promotes an immunosuppressive microenvironment by exhausting HCV-specific $CD8^+$ T cells and increasing $FoxP3^+$ T regulatory cells (Treg) (98). This increased Treg activity dampens other immune cells including lymphocytes, NK cells, and antigen presenting cells (99). Chronically HCV infected cells are characterized by decreased glutathione levels which promote increased oxidative stress and liver injury (100). Prolonged inflammatory state causes hepatocytes to secrete pro-fibrogenic cytokines and to activate myofibroblasts that drive formation of hepatic fibrosis (100).

Patients with chronic HCV who undergo immunomodulatory interventions are described as developing enhanced HCV replication, and while there is no widely accepted definition of HCV reactivation (HCVr) one proposed definition includes an increase in HCV-RNA level of ≥1 log IU/mL from baseline HCV-RNA (101). HCVr is less common and results in less severe consequences than HBVr, but is more likely to occur in patients with hematologic malignancies (78% *vs.* 42%, P=0.002), particularly lymphoma (50% *vs.* 22%, P=0.05) (102). This is especially true following implementation of highly effective direct-acting antiviral (DAA) therapy for HCV treatment (103). Retrospective immunotherapy studies that included patients with HCV-RNA monitoring pre- and post-intervention demonstrated that HCVr occurred in 23–36% of patients (101,102,104).

Viral hepatitis in ICI

Universal screening of patients with newly diagnosed cancer for HBV and HCV is not routine in oncology practice, although most guidelines recommend it. Thus the prevalence of HBV and HCV in those with malignancies is unknown and underreported. In a recent multicenter prospective cohort study of 3,092 patients with newly diagnosed cancers, the observed infection prevalence for previous HBV infection was 6.5% (95% CI: 5.6–7.4%), chronic HBV was 0.6% (95% CI: 0.4–1.0%) and chronic HCV was 2.4% (95% CI: 1.9–3.0%) (105).

PD-1 and CTLA-4 are potent regulators in T-cell mediated pathways and are known to alter activity in chronic HBV and HCV infections (103). The risk of HBVr and HCVr can be explained by the immune activation of hepatocytes which have been chronically infected in an immunosuppressed environment; it is also possible that inhibition of CTLA-4 may result in the activation of Treg, therefore impairing the ability of T cells to further suppress HBV and HCV (106).

Overall, data regarding incidence, prevalence, morbidity, and mortality of HBV reactivation and enhanced HCV replication after initiation of ICI therapy is limited. ICI clinical trials exclude patients with underlying chronic infections due to concerns for reactivation, cellular toxicity, and presumed lack of efficacy (103). The theoretical risk of inefficacy is attributed to chronic viral infections suppressing T cell function (4,32).

Chronic viral hepatitis is characterized by chronic hepatic inflammation, promoting fibrin formation and eventually, cirrhosis (107). This chronically inflamed state promotes hepatocarcinogenesis via mechanisms that inhibit antitumor activity (e.g., impaired NK cell and $CD8^+$ T cell activity) and lead to the development of hepatocellular carcinoma (107). In contrast to many other hematologic and solid-organ tumors, HCC development and maintenance relies heavily on its immune microenvironment, providing

a compelling basis for utilizing ICI therapy for treatment, particularly as advanced HCC is difficult to treat with immunosuppressive chemotherapy (107).

In the IMbrave150 trial, patients with unresectable HCC were treated with either combination atezolizumab and bevacizumab (multikinase inhibitor) or sorafenib with 12-month survival outcomes of 67.2% (95% CI: 61.3–73.1%) and 54.6% (95% CI: 45.2–64%), respectively (60). The study excluded history of autoimmune disease and HBV/HCV coinfection, but the most reported adverse event in atezolizumab/bevacizumab therapy was immune-mediated hepatitis (53% of patients) (60), while viral reactivation was not a reported adverse event (108). This combination immunotherapy has been shown to be more effective in patients with underlying viral liver disease (HBV hazard ratio 0.58, 95% CI: 0.40–0.83; HCV hazard ratio 0.43, 95% CI: 0.25–0.73) compared to non-viral etiology (hazard ratio for death 1.05, 95% CI: 0.68–1.63) (108,109). In the Checkmate 040 trial, 9% of HBV-infected patients (7/82) and 10% of HCV-infected patients (4/39) had virologic breakthrough, defined by the study as 1-log increase in HBV DNA or HCV RNA from baseline (57). In KEYNOTE-224, a non-randomized, open-label trial studying pembrolizumab in sorafenib-refractory patients with HCC, response rate was 16% (95% CI: 7–29%) and did not result in any viral-induced hepatitis flares in the 104 patients included (110). Pembrolizumab monotherapy however, did lead to ILICI in 2.9% of patiens (111).

In the HIMALAYA trial, combination regimen tremelimumab plus durvalumab was compared against sorafenib and results showed an increased median overall survival for treatment of unresectable HCC, 16.43 months (95% CI: 14.06–19.12) versus 13.77 months (95% CI: 12.25–16.13), respectively, with hazard ratio 0.78 (96% CI: 0.65–0.93, P=0.0035) (112). Durvalumab monotherapy was noninferior to sorafenib for the treatment of unresectable HCC, with median overall survival of 16.56 months (95% CI: 14.06–19.12) with hazard ratio of 0.86 (95.67% CI: 0.73–1.03). HBV and HCV accounted for 31% and 27% of the etiologies for chronic liver disease. Although reactivation events were not reported, the most commonly reported immune-mediated adverse event was immune-mediated hepatitis, with 7.5% of patients requiring steroid treatment and 2.3% of patients requiring discontinuation of combination tremelimumab plus durvalumab, comparable to durvalumab monotherapy with 6.4% and 1.3% respectively (112).

HBV and HCV infected patients with HCC who were treated with ICI therapy were compared to non-infected patients and both groups responded similarly to ICI therapy with no significant differences in pre- and post-immune microenvironments (113). Additionally, hepatic viruses were found to be integrated in both malignant and normal hepatocytes, suggesting that the resultant HCC is likely driven more by chronic inflammatory process than by viral infection itself. This meta-analysis confirms that viral status in HCC should not disqualify patients from receiving ICI treatments as outcomes were not significantly different.

Conceptually, via inhibition of these CTLA-4 and PD-1 pathways, activation of T cell response should reverse the T cell exhaustion seen in chronic HBV and HCV thus, promoting viral clearance (106). This immune effect was observed in an *ex vivo* study in which HBV-specific T cell proliferation and increased IFN production was observed after PD-1/PD-L1 blockade (88). The theoretical antiviral effect of ICI therapy is supported by limited data from trials and several cases. In a small retrospective case series, 7 of 9 patients receiving ipilimumab for advanced melanoma with underlying viral hepatitis experienced viral stability, or in 2 cases, HCV regression attributable to ipilimumab alone (114). In an open-label Phase II clinical trial of tremelimumab for the treatment of HCC with underlying chronic HCV, anti-CTLA-4 agent tremelimumab was found to decrease HCV load, from 378×10^3 IU/mL on day 0, to 30.2×10^3 IU/mL on day 120 (n=11, P=0.011), and 1.69×10^3 IU/mL on day 210 (n=6, P=0.017) (115). Viral response, defined as >1 log decrease in HCV load, was seen in 75% (9 of 12) patients (115). In a study of 133 patients, 1.5% (2 of 133) of patients with underlying HBV or HCV developed viral reactivation (98). There is promising evidence to demonstrate an antiviral effect of ICIs, with a small percentage of patients developing paradoxical viral reactivation (98).

Prevention and management of viral hepatitis in ICI therapy

The guideline for screening for chronic HBV infection is in those who are at risk, including persons needing immunosuppressive therapy as they are more likely to develop chronic HBV infection after acute infection (116). Screening is performed using both HBsAg and anti-HBs. The presence of HBsAg establishes the diagnosis of hepatitis B infection. In those who do not have immunity, vaccination against HBV infection is recommended.

In a single-center, retrospective study, 1% of HBsAg

Table 8 Interpretation of screening tests of hepatitis B virus

HBsAg	Anti-HBs	Anti-HBc	Interpretation	Action
+	–	+	Acute or chronic infection	Evaluation and further testing
–	+/–	+	Exposure to HBV; at risk for reactivation	Follow-up as appropriate
–	+	–	Immune due to vaccination	No further action required
–	–	–	At risk for HBV infection	Vaccinate

+, positive; –, negative. HBsAg, hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antibodies; Anti-HBc, anti-hepatitis B core antigen; HBV, hepatitis B virus.

negative patients developed acute hepatitis on chemotherapy compared to 33% of HBsAg positive patients (117). Later reports suggest HBV reactivation occurs in 41–53% (118) of HBsAg-positive, anti-HBc-positive patients and 8–18% (119) of HBsAg-negative, anti-HBc-positive patients receiving anticancer treatments. Thus, screening with anti-HBc to determine prior exposure is recommended in those who will receive immunosuppressive therapies (120,121). Interpretation of screening tests for HBV is summarized in *Table 8*.

There are currently six therapeutic agents approved for the treatment of chronic HBV infection IFN and 5 nucleos(t)ide analogues, which are competitive inhibitors of HBV polymerases and work by inhibiting further HBV DNA synthesis and replication. The 5 available nucleos(t)ide analogues are lamivudine, telbivudine, entecavir, adefovir, and tenofovir but preferred initial therapy is with with Peg-IFN, entecavir or tenofovir (87). Therapy success is determined by biochemical, serological, virological and histological endpoints. Hepatitis B treatment aims to suppress viral replication and can be monitored for efficacy by surrogate markers including the normalization of ALT and loss of HBeAg. Treatment duration with NAs is driven by HBeAg presence, HBV DNA suppression, and complications of liver disease and cirrhosis.

There has been emerging data on antiviral prophylaxis in those undergoing immunosuppressive and immune-modulating drugs. HBsAg-positive patients are at high risk of HBVr thus should receive anti-HBV prophylaxis before the initiation of immunosuppressive therapy (122,123). Patients who receive lamivudine prophylaxis have significantly lower incidence of hepatitis (relative risk =0.40, 95% CI: 0.26–0.63, P<0.0001), and have reduced rate in overall mortality and mortality attributed to HBVr (RR 0.45, 95% CI: 0.29–0.70, P=0.0004 and RR 0.41, 95% CI: 0.20–0.84, P=0.01) compared to those who did not receive prophylactic treatment (124). HBsAg-negative, anti-HBc-positive patients are at lower risk of HBVr and depending on clinical situation can be initiated on anti-HBV prophylaxis or monitored with intention of on-demand therapy at the first signs of reactivation (87). Although antiviral prophylaxis has not been studied in randomized controlled trials, most guidance for anti-HBV therapy is to treat for 12 months following immunosuppressive therapy, especially in the case of B cell deleting therapies (e.g., rituximab) (90,94,121). The prolonged duration of treatment is to account for possible delayed reactivation.

In contrast to the limited effects of successful HBV therapy, achieving complete cure is possible with HCV antiviral treatment. Cure is defined as undetectable HCV RNA 12 weeks after completion of antiviral therapy. Since HCV infection is a curable disease, a one-time, routine, opt-out HCV testing is recommended for all individuals aged 18 years or older (125). Initial screening should be performed with HCV-antibody testing with reflex HCV RNA polymerase chain reaction testing (126). Eradication of HCV infection has numerous health benefits including reduced rates of all-cause mortality, cirrhosis, hepatic decompensation and HCC (127).

The advent of direct acting antiviral (DAA) therapy has revolutionized treatment of HCV and provided therapeutic tools required to strive for elimination (128). Given the highly efficacious nature of treatment, current guidelines recommend antiviral therapy in all adults with acute or chronic HCV infection (125). There are several currently available DAA regimens (*Figure 4*) that provide high sustained virologic response (SVR) rates of >95% (129).

In HCV patients without cirrhosis or those who are treatment-naïve, simplified antiviral regimen with either 8 weeks of glecaprevir/pibrentasvir or 12 weeks of sofosbuvir/velpatasvir is recommended (125). Antiviral treatment recommendations for HCV patients with more decompensated liver disease are more complex. As found in the ASTRAL-4 trial, HCV patients with Child-Pugh-

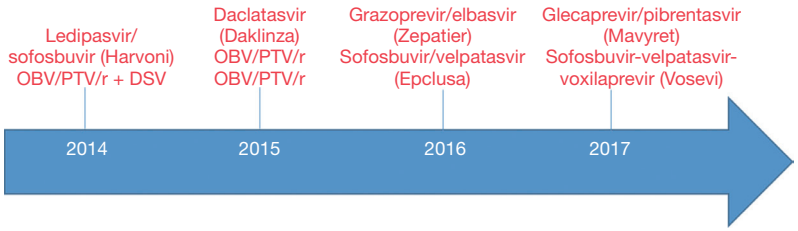

Figure 4 FDA approved direct acting antiviral treatments for hepatitis C virus with >95% SVR. OBV, ombitasvir; PTV, paritaprevir; r, ritonovir; DSV, dasabuvir; FDA, Food and Drug Administration; SVR, sustained virologic response.

Turcotte class B cirrhosis demonstrated lower sustained virologic response 12 weeks after treatment (SVR12), with 83% (95% CI: 74–90%) on sofosbuvir-velpatasvir therapy, and 94% (95% CI: 87–98%) on sofosbuvir-velpatasvir-ribavirin (130). Given the efficacy and tolerability of DAA treatment, HCV treatment can be approached in several ways for patients who undergo immunotherapy. Though there is a paucity of data to support a consensus recommendation for treatment, DAA therapy can be initiated prior to or in combination with immunosuppressive therapy, or initiated at the onset of HCVr in patients who receive HCV-RNA monitoring (102).

This evidence of benefit for screening for HBV and HCV has yet to translate to all guideline-directed practice when implementing ICI therapy. Though there exist some viral screening recommendations for hematologic malignancies and hematopoietic stem cell transplants, guidance for viral screening is limited in other non-hepatic solid organ malignancies utilizing ICI therapy. At a single-institution study at MD Anderson Cancer Center, only 14% of cancer patients starting ICI were screened for HCV (103), despite United States Preventive Services Taskforce (USPSTF) recommendations for once-in-lifetime HCV screening of all adults.

Discussion

ICI therapy has become the mainstay therapy for a large number of cancers including advanced and unresectable HCC. Although ICI therapy has changed the landscape of cancer management, irAEs has been a limitation for overall patient outcomes. ILICI contributes to roughly 5–10% of these irAEs and greater incidence is observed in patients with underlying liver disease, including in the treatment of HCC.

With evolving advancements in the treatment of viral and AIH, it imperative to screen for HBV, HCV, and AIH when initiating ICI to ensure better patient outcomes. Unfortunately, efficacy and safety data in patients with these diseases are lacking, as they have been excluded from major ICI clinical trials due to concern for viral reactivation or AIH flare on initiation of therapy.

We propose a screening algorithm (*Figure 5*) to identify and treat patients with hepatic comorbidities prior to ICI initiation. The authors also encourage early involvement of a hepatology in patients with HCC (*Figure 5A*) and select patients with non-HCC malignancies (*Figure 5B*). This algorithm provides a multidisciplinary approach to ICI therapy and subsequent ILICI management. By utilizing this proposed algorithm and emphasizing routine screening for viral and AIH in patients prior to initiating ICI treatment, substantial improvement in morbidity and mortality can be achieved, allowing for more patients with underlying liver diseases to be safely managed with ICI therapy.

Conclusions

With the growing landscape of ICI therapy, it is crucial to identify and understand the associated risks of therapy to allow for appropriate management. The high morbidity and mortality associated with hepatic toxicity especially highlights the need for careful screening of underlying diseases including autoimmune and viral hepatitis prior to initiation of ICI therapy. As treatment options for advanced and unresectable HCC expand to include more ICI therapy, the prevalence of patients with pre-treatment AIH and chronic HBV and HCV infections will increase. These patients will require close monitoring during treatment and diligent surveillance following its completion.

Use of immunotherapy must be coupled with standard practices of thorough liver evaluation and monitoring. Screening for HBV and HCV infections is paramount in

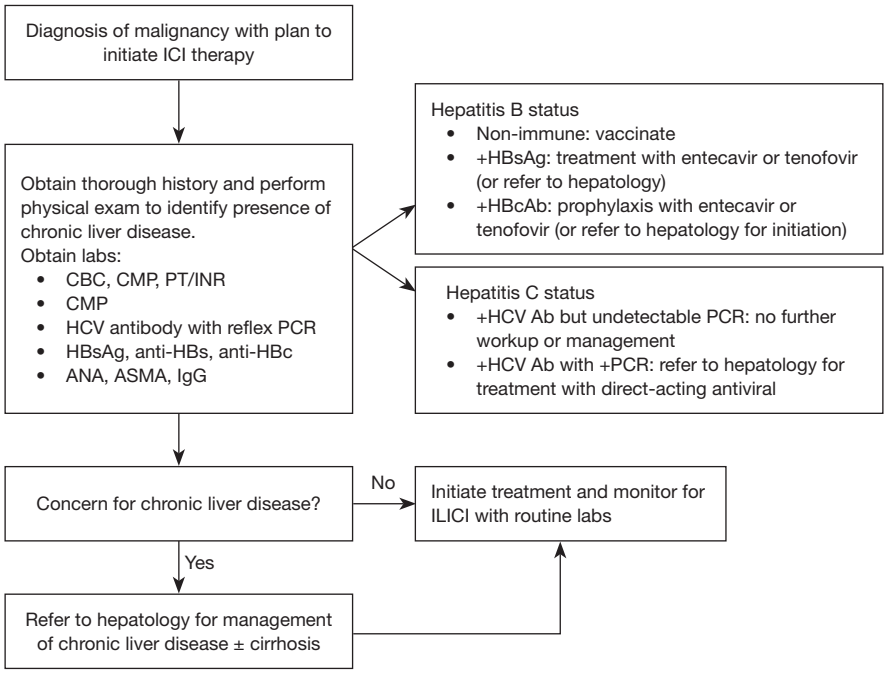

Figure 5 Proposed algorithm for screening and management of liver disease prior to initiation ICI therapy. ICI, immune checkpoint inhibitor; CBC, complete blood count; CMP, comprehensive metabolic panel; PT/INR, prothrombin/international normalized ratio; HCV, hepatitis C virus; PCR, polymerase chain reaction; HBsAg, hepatitis B surface antigen; anti-HBs, anti-hepatitis B surface antibodies; anti-HBc, anti-hepatitis B core antigen; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; IgG, immunoglobulin G; HBcAb, hepatitis B core antigen antibodies; Ab, antibody; ILICI, immune-mediated liver injury caused by ICI.

patients undergoing immunomodulatory therapy in order to avoid severe liver injury, viral reactivation, and even fulminant liver failure.

Currently, literature providing evidence for long-term adverse events and survival benefits is scarce. More longitudinal studies that include patients with underlying autoimmune and viral hepatitis are required to definitively guide management.

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