The Oncologist®

Immune-Related Adverse Events

Diagnosis and Management of Hepatitis in Patients on Checkpoint Blockade

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Many human tumors are recognized by the adaptive immune system, but these spontaneous antitumor responses are typically inadequate to mediate regression. Blockade of immune regulatory "checkpoint" receptors such as cytotoxic T-lymphocyte-associated antigen 4 and programmed cell death 1 can unleash antitumor immunity, resulting in tumor responses that can be durable. Alongside the enormous promise of immunotherapy for cancer, the immune dysregulation of checkpoint blockade has led to a plethora of new autoimmune adverse events. Hepatic toxicity occurs in 1%–17% of patients on immune checkpoint inhibitors, with the precise incidence dependent on both the drug used and the underlying malignancy. Hepatitis is most commonly a low-grade toxicity, but grade 3 and 4 hepatotoxicity does occur. Here we will answer frequently asked questions regarding immune-related hepatitis to assist in the recognition and management of this important condition. ***The Oncologist*** 2018;23:991–997

Key Points

- Immune related hepatitis is a potentially serious complication of checkpoint blockade.
- The differential for elevated liver function tests in patients on checkpoint blockade is broad.
- Diagnostic testing such as viral serologies, liver ultrasound, cross sectional imaging, and liver biopsy may help in the diagnosis of immune related hepatitis in select patients.
- Patients with underlying cirrhosis are an at risk population for whom current grading criteria may underestimate the severity of liver inflammation.
- Severe immune related hepatitis is best managed by a multi-disciplinary team that includes a hepatologist.
- Most patients with immune related hepatitis respond to corticosteroids, but a substantial fraction require treatment with a secondary immunosuppressive agent.

Hepatic Toxicities

Many human tumors are recognized by the adaptive immune system due to their expression of mutated proteins (neoantigens) [1]. Despite this recognition, most spontaneous antitumor immune responses are likely insufficient to cause tumor regression. In part, failure to reject nascent tumors is due to expression of immune regulatory "checkpoint" receptors that inhibit responses from activated T cells [2]. Blocking these checkpoints can unleash antitumor immunity, resulting in tumor response.

Recently, an increasing number of immune checkpoint inhibitors have been U.S. Food and Drug Administration (FDA) approved to treat advanced malignancy, and these therapies have created a paradigm shift in oncology [3–9]. Antibodies against the inhibitory checkpoint receptors cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and its ligand programmed death-ligand 1 (PD-L1) have shown durable responses in a subset of patients [3–9]. Immunotherapy for cancer has enormous promise, but the immune dysregulation induced by these therapies can also lead to adverse events that resemble autoimmune disease [10]. Immune-related adverse events (irAEs) most often affect the skin, gastrointestinal tract and liver, endocrine organs, and lung. The predictors that determine risk for irAEs are not well understood, nor is the relationship between these risks and those that predispose to "sporadic" autoimmunity. This new era of drug development may provide a window into the biology of these regulatory receptors, as well as insights into the onset and progression of sporadic autoimmune disease [11].

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Hepatic toxicity is reported to occur in 1%–17% of patients on immune checkpoint inhibitors [5, 12]. The incidence varies with class of drug and appears to be synergistic in combination therapy targeting both CTLA-4 and PD-1. Hepatitis is most commonly a low-grade toxicity, but grade 3 and 4 hepatotoxicity does occur; similar to the overall incidence, severe hepatotoxicities are also substantially more common in patients on dual checkpoint blockade. Here we will answer a number of frequently asked questions regarding immune-related hepatitis (irH) to assist in the recognition and management of this condition.

Case Vignette

A 66-year-old woman with a history of hypertension, hyperlipidemia, and melanoma with pulmonary metastases received eight cycles of pembrolizumab and was transitioned to ipilimumab after she had documented disease progression. Her transaminases, which were normal prior to starting therapy, increased threefold 3 weeks after initiating ipilimumab. Therapy was held for Ast 170, Alt 488, alk phos 157, and Tbili 0.7. An abdominal ultrasound showed mildly echogenic liver parenchyma with patent hepatic vasculature and no evidence of abdominal metastases. Labs were notable for a normal serum IgG, Anti-Nuclear Antibody (ANA) 1:40, anti-smooth muscle antibody 1:80, antimitochondrial antibody 1:40, and no serologic evidence of acute or chronic viral hepatitis. Due to rising liver chemistries, she was admitted to the hospital and underwent a percutaneous liver biopsy that demonstrated lobular hepatitis with lymphohistiocytic inflammation and hepatocyte injury. She was started on intravenous (IV) methylprednisolone 1 mg/kg b.i.d. and later discharged on an oral prednisone taper. Although her liver chemistries initially improved on oral prednisone, her transaminases later rose during her steroid taper, and she was started on azathioprine 50 mg. Over the course of the next month, her liver chemistries completely normalized on prednisone and azathioprine.

What is an Adequate Assessment Before Starting a Patient on Immunotherapy?

A patient history (noting autoimmune, infectious, or organ-specific disease) is recommended prior to starting a patient on an immune checkpoint inhibitor [13]. Given the possibility of hepatic toxicity, the baseline assessment should include a detailed history of alcohol use, concomitant medications including acetaminophen, and herbal supplements.

During the pretreatment physical exam, one should look for signs of advanced liver disease including the presence of spider angiomata, palmar erythema, gynecomastia, ascites, caput medusa, splenomegaly, or jaundice. Although potentially suggestive of advanced liver disease, these findings should be interpreted in the context of the patient's underlying malignancy and other known chronic diseases

Blood tests to consider include complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, Hemoglobin A1c (HbA1C), free thyroxine (T4), creatine kinase (CK), and an infectious disease screen with hepatitis B virus surface antigen (HBsAg), surface antibody and core antibody (HBsAb), hepatitis C virus antibody (HBcAb), cytomegalovirus antibody (HCVAb), CMV antibody, T-spot test, human immunodeficiency virus testing (HIV), and a fasting lipid profile [13]. Liver chemistries should be drawn at baseline and at the time of each immunotherapy cycle. Elevated aminotransferase levels are most often the only indication of irH.

Baseline disease assessment with imaging is standard to evaluate disease burden in the liver for many malignancies. If abdominal imaging obtained as part of cancer staging is suggestive of underlying cirrhosis, confirmation of the diagnosis by liver biopsy or hepatic elastography (in patients without hepatic metastases) should be considered, although these tests to not necessarily need to be completed prior to initiation of therapy. Patients with underlying cirrhosis may benefit from more careful monitoring or earlier involvement of hepatology if they develop changes in liver chemistries during immunotherapy treatment.

What Hepatic Immune-Related Adverse Events Have Been Reported and How Do They Present?

There is marked variability in the clinical and histopathologic presentation of irH. Patients can be asymptomatic, present with nonspecific symptoms such as fever and fatigue, or have rapid progression and fulminant disease [14]. Asymptomatic elevations in the transaminases is the most common initial presentation [15].

Clinical trials have classified hepatic toxicity with a range of terminology. Categories include elevated alkaline phosphatase or aspartate aminotransferase, increased transaminases, or hepatitis. Although the incidence of severe toxicity is infrequent with single-agent therapy, it seems to be synergistic in patients on combination immune checkpoint inhibitors (Table 1). The highest rate of severe hepatic toxicity was seen in a combination halted for further development, dacarbazine with ipilimumab, which reported grade 3/4 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) rates over 17% [21].

The Common Terminology Criteria for Adverse Events (CTCAE) is currently used to categorize the severity of immune-related adverse events (Table 2). Importantly, these criteria were created for patients on chemotherapy and therefore can underestimate the severity of inflammatory hepatitis. A quantitative increase in liver chemistries is not the sole marker for imminent severe disease. Of note, in sporadic autoimmune hepatitis, the level of transaminases does not always correlate with histologic extent of injury, particularly in the setting of hepatic fibrosis [22].

In addition, the CTCAE simplifies diverse pathologies. As a result, one could misclassify the severity of illness, missing more severe disease with lower liver chemistries; therefore, a grading system specifically for immuno-oncology needs to be considered. In lieu of this, at our institution, we consider any sign or symptom of liver failure or progressive rise in bilirubin grade 3 disease, and we consider alkaline phosphatase an independent classifier of grade, as alkaline phosphatase can be a leading indicator of biliary obstruction or inflammation [23]. Clinical features of concern include a rapidly rising alkaline phosphatase, coagulopathy, development of hepatic encephalopathy (mild confusion or asterixis to coma), ascites, or other symptoms of liver disease (pruritis, jaundice, petechiae, unexplained lactic acidosis).

Patients with underlying cirrhosis are a vulnerable population in which the CTCAE also likely underestimates the underlying disease severity. This is now more relevant after the FDA approval of nivolumab for patients with hepatocellular

Table 1. Severity of liver toxicity by drug, by cancer type

Cancer type and drug	Hepatitis[a]		AST		ALT	
	All Gr	Gr 3/4	All Gr	Gr 3/4	All Gr	Gr 3/4
Melanoma						
Pembrolizumab [12] every 3 wk	5/277 (1.8%)	5/277 (1.8%)				
Nivolumab [5] every 2 wk			12/313 (3.8%)	3/313 (1%)	12/313 (3.8%)	4/313 (1.3%)
Ipilimumab [5, 12] every 3 wk	3/256 (1.2%)		11/311 (3.5)	2/313 (.6%)	12/311 (3.9%)	5/311 (1.6%)
Ipilimumab + Nivolumab [5] 1 mg/kg Nivolumab + 3 mg/kg ipilimumab			48/313 (15.3%)	19/313 (6.1%)	55/313 (17.6%)	26/313 (8.3%)
Lung						
Pembrolizumab [16]	1/339 (<1%)	1/339 (<1%)				
Nivolumab [7, 8]						
Ipilimumab + Nivolumab [17] Nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 12 wk ($n = 38$)			1/38 (2.6%)		1/38 (2.6%)	
Hepatocellular carcinoma						
Nivolumab 3 mg/kg every 2 wk [18]			10/48 (21%)	5/48 (10%)	7/48 (15%)	3/48 (6%)
Colon cancer dMMR/MSI-H						
Nivolumab 3 mg/kg every 2 wk [19]			5/74 (7%)		3/74 (4%)	1/74 (1%)
Gastric cancer						
Nivolumab 3 mg/kg every 2 wk [20]	1/330 (<1%)	1/330 (grade 5; <1%)	11/330 (3%)	2/330 (1%)	7/330 (2%)	1/330 (<1%)

[a]Headings refer to the adverse events documented as reported in the cited trials.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; dMMR, deficient mismatch repair; Gr, grade; MSI-H, micro satellite instability high; wk, week.

Table 2. Grading of liver function tests

Liver Test	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase	>ULN–2.5 × ULN (<200)	>2.5–5.0 × ULN (200–400)	>5.0–20.0 × ULN (>400)	>20.0 × ULN
Bilirubin	>ULN–1.5 × ULN	>1.5–3.0 × ULN	>3.0–10.0 × ULN	>10.0 × ULN
Aspartate aminotransferase	>ULN–3.0 × ULN (<100)	>3.0–5.0 × ULN (100–200)	>5.0–20.0 × ULN (>200)	>20.0 × ULN
Alanine aminotransferase	>ULN–3.0 × ULN (<100)	>3.0–5.0 × ULN (100–200)	>5.0–20.0 × ULN (>200)	>20.0 × ULN

Adapted from Common Terminology Criteria for Adverse Events, ULN based on institutional reference lab ranges; suggested values in parentheses are based on ideal values for an otherwise healthy individual.
Abbreviations: ULN, upper limit of normal.

carcinoma following sorafenib [18]. The CTCAE grading criteria may not be adequate in patients with cirrhosis who have fewer healthy hepatocytes at baseline, leading to both lower transaminases at equivalent levels of inflammation and a lower threshold for hepatic decompensation. Monitoring of Child's class over the course of treatment is critical, and changes in Child's class should be handled as serious adverse events regardless of the degree of change in transaminases.

Right-upper-quadrant pain is a rare presentation for isolated irH and can indicate biliary obstruction, which would necessitate further investigation. Rapid distention of the liver capsule in the setting of severe hepatitis, or tumor pseudoprogression, is a less common cause of liver-related pain. Because checkpoint blockade can lead to multiple inflammatory toxicities simultaneously, patients with hepatitis and abdominal pain should also be investigated for concurrent inflammatory pathology within the gastrointestinal tract [11].

What is the General Time of Onset of Hepatic irAEs?

The median onset of transaminase elevation is approximately 6–14 weeks after starting ICI treatment [10, 14, 24–26]. However, median time to onset appears variable depending on underlying malignancy and type of drug. Timing of onset of hepatitis after nivolumab in lung cancer (median 25 weeks, range 4–31) differs from melanoma (median 4 weeks, range 1–23 weeks) [27] and is longer than median onset with pembrolizumab (median 19 weeks, range 3–93) [27]. In our experience, hepatitis can also become unmasked in the setting of a steroid taper for other immune-related adverse events. Because of the range of reported presentations, we do not feel that timing of onset is useful diagnostically to distinguish checkpoint blockade-induced hepatitis from other potential causes of transaminase elevation in these patients, and it did not figure into the evaluation in the case presented.

What are the Critical Components of the History, Physical, and Evaluation?

The differential includes a range of conditions associated with liver test abnormalities in cancer patients. Diagnosis is determined by clinical and laboratory findings, in addition to histopathologic features when liver biopsy is necessary.

The critical components of the history include (a) quantity and duration of alcohol consumption, (b) risk factors for hepatitis B and C (endemic area, sexual history, intravenous drug use, tattoos, transfusion history), (c) risk factors for nonalcoholic fatty liver disease (obesity, diabetes, hyperlipidemia), (d)

previous chemotherapy, and (e) use of other hepatotoxic drugs, including herbal medications, acetaminophen, and other medications purchased over the counter.

Patients typically present without symptoms or with nonspecific symptoms such as fatigue. Pruritis can occur in association with cholestatic hepatitis but should raise the suspicions for an alternative etiology such as drug-induced liver injury. Because of the risk of overlapping irAEs, many patients also present with symptoms unrelated to their hepatitis, but related to their underlying therapy, such as nausea, diarrhea, or joint pain.

Hepatitis from checkpoint blockade typically has no physical exam findings. Signs of severe liver injury on physical exam should be evaluated (asterixis, ascites, caput medusa, hepatomegaly, jaundice, scleral icterus). Fevers should prompt a workup for infection.

The differential for hepatitis in a patient with cancer on checkpoint blockade is broad, and alternative diagnoses should be carefully considered.

- Disease progression (or pseudoprogression).
- Acute infections (Epstein Barr Virus (EBV), CMV, hepatitis A/B/C, adenovirus), particularly in patients on immune suppression for previous irAE or other reasons.
- Drug-induced liver injury in any patient taking a new medication; this is one of the main diagnoses that can be assessed by liver biopsy. Common offenders include acetaminophen and acetaminophen combination medications (i.e., percocet), antibiotics, statins, targeted therapy, chemotherapy, nitrofurantoin, methyldopa, diclofenac, and herbs such as Sho-saiko-to. The NIH LiverTox webite (https://livertox.nih.gov) provides up-to-date information on liver injury caused by prescription and nonprescription medications, herbs, and dietary supplements. For patients who appear systemically ill with elevated liver chemistries, fever, rash, eosinophilia, and lymphadenopathy, more severe drug reactions such as drug reaction with eosinophilia and systemic symptoms should be considered.
- Thromboembolism associated with metastatic cancer such as portal vein thrombosis, Budd Chiari syndrome, and hepatic sinusoidal obstruction syndrome. Hepatic ultrasound with dopplers to exclude clot should be considered with $\geq$grade 2 Liver Function Tests (LFT)s.
- Shock liver has a sudden onset and rapid resolution without treatment; as hypotension is not always documented clinically, this diagnosis should be considered for all patients at risk for hepatic hypoperfusion.
- Alcohol-induced hepatitis should be specifically investigated by history and potential blood alcohol testing in any patient with an AST/ALT ratio greater than 1.
- Myositis is an uncommon irAE but should be considered in patients with dramatic AST elevations relative to ALT and in patients presenting with muscle pain or severe fatigue.
- Immune-mediated hepatitis. Although a common cause of liver test elevations in patients on immunotherapy, treating a presumptive diagnosis without considering alternatives can expose patients to unnecessary risk.

Patients with serologic evidence of chronic infection with hepatitis B (HBsAg positive) or hepatitis C (HCV RNA positive) are at increased risk for worsening viral hepatitis in the setting of immune suppression, and the influence of checkpoint blockade on these infections is poorly understood. Viral hepatitis should be strongly considered in any chronically infected patient whose liver chemistries worsen during immunotherapy treatment or while on immunosuppressive medications. Patients with isolated HBcAb positivity with negative HBsAg are at extremely low risk for reactivation, although repeat HBsAg testing could be considered in these patients if they have elevations in their liver chemistries. Antiviral therapy is generally well tolerated for both hepatitis B and hepatitis C and may be indicated in some instances in conjunction with a hepatologist; these include patients with a high likelihood of long-term survival, those with evidence of substantial ongoing active viral hepatitis, and those for whom treatment with a Tumor Necrosis Factor (TNF)-α blocking biologic is otherwise indicated.

The utility of liver biopsies in patients with suspected irH is incompletely understood, and guidelines are based on expert opinion. Several pathologic subtypes have been described for patients with suspected hepatitis on checkpoint therapy. These include a "classic" panlobular lymphocytic hepatitis, zone 3 hepatitis with central vein damage and endothelial inflammation, cholangitis, bile duct injury, nonalcoholic steatohepatitis, and fibrin ring granulomas (with PD-1) [14, 24, 26]. These different histologic subtypes likely represent manifestations of distinct immune pathologies. Whether these disinct pathologies alter response to treatment is unknown, although clearly a substantial fraction of cases of checkpoint hepatitis do not respond to first-line corticosteroids.

At our institution, we perform biopsies on most patients with grade 3 or higher hepatitis and on selected patients with lower-grade complications. Factors that should be considered prior to obtaining a biopsy are the use of other potentially hepatotoxic medications in addition to immunotherapy, use of investigational combinations, presence of hepatic metastases, cholestatic hepatitis, failure to respond to corticosteroids, and bleeding risk. Image-guided percutaneous liver biopsy has a risk for subcapsular hemorrhage that is reported to be 0.8%–1.7% in patients with normal coagulation and platelet counts, although the actual risk is operator dependent. Most subcapsular hemorrhages will resolve with supportive care, and mortality from these injuries is exceptionally low. For patients deemed at increased risk for percutaneous biopsy (i.e., those with coagulopathy, infection of the overlying skin, or large-volume ascites) and who have normal neck anatomy, a transjugular biopsy has a lower risk for serious complications (0.6%) and may be appropriate. In the case vignette, the patient presented with grade 3 hepatitis and we made the decision to confirm the diagnosis of irH prior to beginning steroids as she was a low-risk biopsy candidate, and we were able to obtain a biopsy shortly after presentation.

American Society of Clinical Oncology guidelines recommend consideration of liver autoantibody testing (Anti-Nuclear Antibody (ANA), Anti-Smooth Muscle Antibody (ASMA), and liver/kidney microsomes [LKM]) [28]. Sporadic autoimmune hepatitis occurs in two groups. Type 1 autoimmune hepatitis is classically characterized by ANA and/or ASMA circulating antibodies, although low titers of these autoimmune markers $\leq$1:80 are common in other chronic liver diseases such as fatty liver disease. Type 2 autoimmune hepatitis is associated with antibodies to LKM. Positive autoantibodies are uncommon in irH, although in the case presented, ASMA was borderline

Table 3. Recommended hepatic workup

Liver Test	Grade 1	Grade 2	Grade 3	Grade 4
AST and ALT	SITC/ESMO/ASCO-NCCN- Continue ICU, check LFT 1–2 times weekly	SITC/ASCO-NCCN • Hold ICI • Check LFTs biweekly, workup with viral, autoimmune studies investigate new metastasis, clot • Corticosteroid 0.5–1 mg/kg with at least 1-month taper • Resume ICI when LFTs are grade 1 and corticosteroid taper is 10 mg/day or less • SITC recommendations state liver biopsy is optional ESMO • Hold ICI • Review medications (statins, antibiotics, EtOH) • Workup—LFT, INR, albumin every 3 days, hepatitis A/B/C serology, hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies, consider imaging • If rising on recheck, start oral prednisolone 1 mg/kg • Once G1 wean over 2 weeks, once <10 mg, resume	SITC/ASCO-NCCN: • Permanently discontinue ICI • Monitor CMP every 1–2 days, corticosteroid 1–2 mg/kg/day. • SITC: If no improvement after 3 days, trial mycophenolate mofetil. • ASCO-NCCN: If no improvement after 3 days, trial mycophenolate mofetil or azathioprine • If LFTs improve, taper over 4 weeks • SITC recommendations state consider liver biopsy • ASCO-NCCN states if no improvement or for patients on combination therapy, refer to hepatologist for further pathologic evaluation of hepatitis ESMO • Stop ICI • Workup as in grade 2 with US with Doppler • ALT/AST <400 and nl bili/INR/albumin – oral prednisolone 1 mg/kg • ALT/AST >400 or raised bilirubin/INR/low albumin (IV methylprednisolone 2 mg/kg) • IV until grade 2, then oral with wean over 4 weeks • Rechallenge only with GI involvement for G3. • Low threshold to admit to hospital	SITC • Identical recommendations as in grade 3 ASCO-NCCN • Permanently discontinue ICI • Monitor labs daily, consider hospitalization • Administer methylprednisolone 2 mg/kg/day • Hepatology consult if no improvement • Consider mycophenolate mofetil if no improvement after 3 days • Consider transfer to tertiary care facility • Corticosteroid taper can be attempted 4–6 weeks when symptoms improve to G1 or less, optimal duration unclear ESMO • Stop ICI • Methylprednisolone 2 mg/kg • Consider liver biopsy, hepatology consult
Bilirubin	Continue ICU	Our recommendation: Hold ICI		
ALP	Continue ICU	Our recommendation: Hold ICI		
	Our thoughts: If bili is elevated or symptoms, consider escalating the grade of toxicity (RUQ pain, edema/ascites, pruritis). Elevated INR, hepatic encephalopathy, new ascites is severe toxicity regardless of ALT/AST. If persistent grade 1, persist with additional workup	Our thoughts: If bili is elevated or symptoms, again consider escalating grade. For complete workup, recommend RUQ US with Doppler with consideration of cross-sectional imaging if there is concern for new metastatic disease, CK, confirm ALP elevation with GGT, send HepA Ab, HepB sAg/sAb/cAb, HepC Ab. If additional risk factors/exposures are present, send HepB cAb, IgM, HepA IgM, HepC PCR. Consider infectious workup (EBV/CMV) especially in immune-compromised hosts. Consider MRCP in patients with symptoms of biliary obstruction (RUQ pain, crampy pain with eating, ALP elevation) Note, autoimmune serologies will not change management, and it is unclear if serologies are pathogenic in autoimmune hepatitis or if they are good biomarkers for patients that will respond to steroids	Our thoughts: Taper corticosteroids by 10 mg/week, and the decision to permanently discontinue immunotherapy should be etiology specific. Grade 3 or higher is the right time to involve someone experienced with checkpoint blockaded-induced hepatitis. Consider admission for IV steroids (although a trial of oral steroids is reasonable), for accelerated workup and symptom management. If the biopsy is not diagnostic for checkpoint hepatitis and there is no tumor-related anatomic cause (mets, SIRT), ensure a hepatologist is involved.	

Adapted from published guidelines [13, 24, 32–34] and Common Terminology Criteria for Adverse Events.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; CK, creatine kinase; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; EBV, Epstein Barr virus; ESMO, European Society for Medical Oncology; EtOH, ethyl alcohol; GGT, Gamma-glutamyl transferase; GI, gastrointestinal; ICI, immune checkpoint inhibitor; ICU, intensive care unit; INR, international normalized ratio; IV, intravenous; LCI, liver cytosol 1; LFT, liver function tests; LKM, liver kidney microsome; LP, liver-pancreas; MRCP, magnetic resonance cholangiography; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; RUQ, right upper quadrant; SIRT, selective internal radiation therapy; SITC, society for immunotherapy of cancer; SLA, soluble liver antigen; SMA, smooth muscle antibody; US, ultrasound.

positive. The presence (or absence) of these antibodies in patients with irH does not change management, and their clinical significance in this population is unknown.

What is the Typical Treatment?

Treatment of patients with severe liver disease is complex and is managed best through a multidisciplinary team that includes practitioners who are familiar with the underlying cancer and the immunotherapeutic agent, as well as experts in hepatology and liver pathology (Table 3). This approach may increase the chance that alternative diagnoses will be captured and can improve symptomatic management.

Corticosteroids are first-line therapy for suspected or established irH. No trials have directly addressed corticosteroid dose, nor has the effectiveness of any corticosteroid regimen been clearly established. Most centers use steroid dosing regimens borrowed from the treatment of other irAEs associated with checkpoint blockade or from the treatment of spontaneous autoimmune hepatitis. For outpatients, we typically start by treating with prednisone 60 mg daily and taper slowly over a period of 2 months. For hospitalized patients, patients with grade 4 disease, or patients who incompletely respond to prednisone, we consider IV solumedrol 0.5–1 mg/kg b.i.d. For patients who incompletely respond to corticosteroids, or who flare during a steroid taper, several other agents have been reported to have efficacy in the second line. These include azathioprine (1–2 mg/kg), mycophenolate mofetil (500–1,000 mg b.i.d.), or tacrolimus (dosed based on blood trough levels targeting 8–10). Importantly, before using azathioprine, the FDA recommends testing for Thiopurine S-methyltransferase (TPMT) genotype or enzyme function, as patients with decreased TPMT activity are at high risk for developing life-threatening bone marrow suppression. Lastly, a case of fulminent hepatitis after ipilimumab resolved with antithymocyte globulin therapy [25]. At this time, the relative efficacy of these agents for irH is unknown, and there are no evidence-based criteria for choosing among them. Both tacrolimus and mycophenolate are used as immune suppressants in liver transplant. Azathioprine is generally first-line maintenance therapy for sporadic autoimmune hepatitis and was selected in the case vignette above for this reason.

Infliximab is associated with a rare syndrome of immune-mediated hepatitis and for this reason is not recommended as therapy for irH. Although given the rarity of this side effect, the presence of irH should not be considered an absolute contraindication to infliximab treatment in patients who develop other life-threatening irAEs that are steroid nonresponsive, such as checkpoint colitis [29].

What are Considerations with Using Steroids?

Corticosteroids are broadly immune suppressive, with a range of side effects, and the effect on antitumor immunity in patients is unknown. In animal models, corticosteroids clearly inhibit effective antitumor responses, but retrospective analyses of patients suggest that corticosteroid use is not associated with decreased overall survival compared with untreated patients [30]. We recommend avoiding empiric corticosteroid use until other diagnoses have been effectively excluded, provided this can be done rapidly. This approach limits steroid side effects, may improve antitumor responses, and may lead to more rapid recognition of the underlying problem. For example, transaminases may fall in drug-induced liver injury while holding specific medications, but without any biopsy/confirmation, this could be attributed to empiric corticosteroid use, leading to a prolonged corticosteroid course and possible re-exposure to the inciting medication.

What is the Prognosis?

Most patients with irH will have resolution of the hepatitic injury with immune suppression, and the long-term prognosis appears to be good. This was the case with the patient presented above. Whether some subset of patients with prior irH remain at risk for complications in the future is unknown.

Importantly, we have minimal data on the risks and outcomes of irH in the setting of cirrhosis, and these patients should be managed cautiously and in conjunction with a hepatologist.

Who Can You Re-Treat?

Any patient with a diagnosis of hepatitis that is not directly related to checkpoint blockade could be considered for retreatment. Rapid resolution of transaminase elevations may point to specific etiologies and should be considered in retreatment decisions. Grade 1 hepatitis does not require discontinuation of treatment. Patients who develop hepatitis with treatment targeting one pathway (e.g., CTLA-4) are not necessarily going to develop irH from treatment targeting another pathway (PD-1/PD-L1) [31]; however, retreatment of irH patients with drugs from the same class (i.e., nivolumab and pembrolizumab) is not recommended. At present, there are no therapies that have been tried concurrently with checkpoint blockade to suppress irH, but this is an attractive area for research.

Conclusion

The hepatic toxicities associated with checkpoint blockade are heterogenous, with a wide range of underlying pathophysiologies of which immune-mediated disease is a significant fraction, but far from the only etiology. Biopsy is the gold standard for diagnosis of liver disease and should be considered in any patient with changes in liver chemistries that would prompt changes in management. The incidence of irH varies with the class of drug and appears to be synergistic with combination therapy targeting CTLA-4 and PD-1. This is likely to be an increasing issue as more combination clinical trials begin, including those with chemotherapy or targeted therapy. Baseline assessments are essential, but even substantial underlying liver disease does not preclude treatment. Greater caution should be taken with patients who have cirrhosis or those with liver dysfunction prior to treatment. Diagnosing impending liver failure is challenging, and CTCAE does not accurately capture severity. Time to onset varies, so clinical suspicion must stay elevated. Even when the diagnosis of irH is clear, management strategies have not been optimized. Through collaborative efforts, we have an opportunity to characterize this disease far more completely, develop more tailored treatments, and establish more meaningful guidelines both for immune-mediated hepatotoxicity and potentially for sporadic autoimmune hepatitis.

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