Immune checkpoint inhibitors and liver immune-related adverse effects: A comprehensive review of diagnosis and management

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Abstract

Immune checkpoint inhibitors (ICI) have greatly improved the management of advanced solid tumors with proven efficacy in overall survival rates. However, their increasing use is associated with a number of immune-mediated adverse events in almost every system organ. Liver toxicity, although rare, can be occasionally severe with the development of severe immune-mediated hepatitis. The current grading system assessing the severity of liver toxicity is suboptimal, overestimating the true incidence of severe hepatitis, and research should be guided towards this direction. Management includes the introduction of corticosteroids in cases of grade 2 or greater hepatitis but there are reports of spontaneous resolution without the use of immunosuppressive treatment. Thus, treatment algorithms need to be revised and predictive factors of spontaneous resolution need to be discovered. This review focuses on liver complications related to ICI treatment discussing incidence, diagnosis and treatment strategy currently used in this setting.

Key words: *Immune checkpoint inhibitors; Immune-mediated hepatitis; liver toxicity*

INTRODUCTION

In the last decade, the introduction of immune checkpoint inhibitors (ICIs) in the therapeutic management of different cancer types including unresectable or metastatic melanoma, advanced hepatocellular carcinoma and metastatic non-small cell lung cancer [1-4], has both changed treatment algorithms and improved overall survival rates in this setting. Since the approval of ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibody) for the treatment of unresectable or metastatic melanoma [3], many other ICIs have been introduced and their therapeutic indications have been expanded in other tumor types.

The molecular targets of ICIs are immune checkpoints, i.e., CTLA4, programmed cell death protein 1 (PD-1) and its ligands (PD-L1/PD-L2), which normally have an inhibitory effect on T-cell activation preventing auto-immunity, thus providing immunological tolerance to self-antigens [5, 6]. By inhibiting immune checkpoint signaling, T-cell activity is restored and the immune tolerance against specific tumor antigens is reversed thus promoting a durable anti-tumor immune response.

However, the abovementioned interference with the natural immunological tolerance can result in the development of various systemic toxicities due to the loss of T-cell inhibition leading to abnormal host immune responses [7]. These toxicities are called immune-related

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adverse events (irAEs) and can potentially affect every organ system (most commonly the skin, the gastrointestinal tract and the liver, and the endocrine system). They can mimic other immune-mediated disorders and have been associated with severe and sometimes fatal outcomes in cases of delayed diagnosis.

The aim of this review was to focus on the immune-related hepatic complications resulting from ICI treatment as well as its management, which is mostly based on expert opinions. Due to the lack of randomized controlled trials on this topic, it was impossible to conduct a systematic review.

METHODS

MEDLINE databases were searched for eligible studies from August 2006 to April 2022 using the textwords "Checkpoint inhibitors" or "immune checkpoint inhibitors" or "anti-CTLA4" or "anti-CTLA-4" or "anti-PD1" or "anti-PDL1" or "ipilimumab", or "pembrolizumab" or "nivolumab" and "hepatitis" or "liver toxicity" or "toxicity" or "liver" or" adverse event" or "immune-related adverse event". All relevant review articles (English) were manually searched, and all original studies were retrieved from them.

Epidemiology of liver irAEs

The overall incidence of irAEs is ranging between 15% and 90%, and as already mentioned, every organ system can be potentially affected [7-9]. The dermatological and gastrointestinal (colon, small intestine, liver and pancreas) irAEs are the most common toxicities [10-12]. The incidence and severity of irAEs seem to be unaffected by the tumor type [13]. However, CTLA inhibitors are more frequently associated with irAEs compared to anti-PD1/PDL1 agents, and these toxicities are usually more severe. In a meta-analysis [8] of 1265 patients from 22 clinical trials, the overall incidence of all-grade irAEs in oncologic patients receiving anti-CTLA4 antibodies (ipilimumab and tremelimumab) was 72 % (95 % CI, 65–79 %) (high-grade irAEs, 24 % (95 % CI, 18–30 %)); this association was found to be dose-dependent. In a systematic review of 23 studies comprising 3284 patients in the PD-1 group and 2460 patients in the PD-L1 group [14], the overall incidence of all-grade adverse events was 64% (95% CI, 63%-66%]) and 66% (95% CI, 65%-69%) for PD-1 and PD-L1 inhibitors ((high-grade irAEs, 13% (95% CI, 12%-14%) and 21% (95% CI, 19%-23%)), respectively. The risk increases substantially for patients treated with both CTLA4 and PD1/PDL1 inhibitors, implying an additive toxicity when combination is used [15]. On the other hand, in a retrospective study [16] which aimed to assess the safety profile of nivolumab monotherapy in patients with advanced melanoma, the objective response rate was significantly higher in patients that demonstrated irAEs compared to those that did not (48.6% s 17.8%, $p<0.001$).

Regarding liver irAEs, the incidence of all-grade and high-grade immune-mediated hepatitis in ICI users is around 5% and 1-2%, respectively [17]. This incidence increases at 25% and 8-10%, respectively, when combination of ICIs is used [15, 18]. It seems that the risk is higher in ICI-users treated for hepatocellular carcinoma compared to those treated for non-liver cancers [19].

Dermatological irAEs usually occur at around four weeks after initiation of treatment, together with gastrointestinal ones (at around six weeks), whereas liver toxicity appears later at approximately 8-12 weeks after starting ICI treatment [16]. However, liver abnormalities, as all other irAEs, can occur even after longer time periods following initial administration [20].

Grading of severity of liver irAEs

The severity of irAEs is more commonly graded using the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [21]. Depending on these criteria, the severity is graded on a scale of 1 to 5 as follows: grade 1 (mild toxicity), grade 2 (moderate toxicity), grade 3 (severe toxicity), grade 4 (life-threatening) and grade 5 (death). The grading of severity of ICI-related hepatitis is depicted in Table 1.

This grading scale has the advantage of stratifying treatment management and thus, it has been extensively used in clinical trials of ICIs allowing comparisons between studies; however, it is accompanied by several drawbacks, most importantly the overestimation of the incidence and severity of symptoms by physicians [6]. According to the European Association for the Study of the Liver (EASL) guidelines [22], drug-induced liver injury is considered severe if the elevation of transaminases is accompanied with an increase in bilirubin (Hy's law), whereas the level of elevation of liver enzymes alone is not sufficient to reflect the severity of liver injury. This is not in accordance with CTCAE criteria [21], where grade 4 hepatotoxicity is defined as very high levels of transaminases without concomitant increase in bilirubin. Consequently, the CTCAE grading system is considered suboptimal and more research is needed in the setting of severity stratification.

Table 1. *Grading of severity of ICI hepatitis (National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0).*

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hepatitis	AST or ALT 1 3×ULN and/or T-BIL 1 1.5×ULN	AST or ALT 3 5×ULN and/or T-BIL 1.5 3×ULN	AST or ALT 5-20×ULN and/or T-BIL 3-10×ULN	AST or ALT >20×ULN and/or T-BIL >10×ULN	Death

AST: aspartate aminotransferase, ALT: alanine aminotransferase, t-bil: total bilirubin, ULN: Upper Limit of normal

Clinical presentation of liver irAEs

ICI hepatitis is mostly asymptomatic and usually follows a hepatocellular pattern of liver injury characterized by elevations of aminotransferases (ALT and AST) with or without mildly increased total bilirubin levels [23-25]. Cases of cholestatic liver injury have been reported but they are not the rule [26]. Symptoms like fever, malaise, abdominal discomfort or jaundice are rare. Moreover, fulminant hepatitis causing acute liver failure is very uncommon with an incidence of about 0.4% [27]. Taking the abovementioned into account, the diagnosis of ICI-hepatitis is mostly incidental following routine blood testing.

Although an immune-mediated hepatitis, ICI hepatitis should be dissociated from autoimmune hepatitis. The histological features of ICI hepatitis are usually portal and periportal hepatitis and hepatocellular necrosis (mostly centrilobular) with infiltration by lymphocytes, plasma cells and eosinophils, thus resembling acute viral or autoimmune hepatitis [28, 29]. However, high titles of anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) and other autoimmune hepatitis-related auto-antibodies are usually absent and ICI hepatitis typically responds to drug discontinuation and one course of immunosuppressive treatment without recurrence, thus is differentiated from idiopathic autoimmune hepatitis [30, 31]. Furthermore, the presence of cirrhosis, emperipolesis and rosette formation are hallmarks of autoimmune hepatitis, not typical in ICI-related hepatitis [22, 31]. Interestingly, one histological pattern specific for patients under treatment with anti-CTLA4 agents is that of non-necrotizing granulomatous hepatitis, whereas liver injury by anti-PD1/PDL1 has a more heterogenous pattern without the presence of granulomas [23, 32]. Bile duct injury with the presence of cholangitis in histological specimens following treatment with ICIs has also been reported and is usually mild [33]. Other unusual presentations demonstrated in case reports are sclerosing cholangitis, nodular regenerative hyperplasia, sinusoidal obstruction syndrome and vanishing bile duct syndrome [34].

Diagnosis of liver irAEs

The diagnosis of ICI-related hepatitis is mostly a diagnosis of exclusion. The initial approach includes detailed medical history (including alcohol and concomitant drugs/herbs use) and physical examination. Infectious causes of abnormal liver function tests (i.e., viral hepatitis A, B, C, and E, Epstein-Barr virus, Cytomegalovirus, Herpes Simplex virus) should be excluded [22, 35-37]. Auto-antibodies including ANA, ASMA, anti-mitochondrial antibodies (if cholestatic injury pattern), liver-kidney microsomal type 1 (LKM-1) antibodies, as well as quantitative assessment of immunoglobulins should be assessed. An abdominal ultrasound is also part of the initial work-up to exclude vascular thrombosis, hepatic metastases, liver cirrhosis or biliary obstruction.

The question is if liver biopsy is indicated in the initial assessment of patients under ICI treatment presenting with abnormal liver function tests [19]. As mentioned before, liver histology can assist in both the diagnosis of ICI-related liver toxicity and the assessment of severity of liver injury; thus, it can guide treatment management. Currently, liver biopsy is reserved for patients with grade 3 or greater liver toxicity and/or to exclude alternative diagnoses.

Management of liver irAEs

According to the EASL recommendations [22], which rely on clinical experience and the management of autoimmune hepatitis, before the initiation of treatment with ICIs, baseline liver parameters and the patient's lipid profile should be assessed. Potential confounding factors such as pre-existing liver diseases and presence of liver metastases, as well as viral infections (HIV, HBV, HCV, HEV) should be excluded. Underlying autoimmune hepatitis or other autoimmune disorders should be investigated.

Following initiation of treatment, liver function tests

should be monitored every two weeks for the first 8 to 12 weeks of treatment, and then every four weeks [22].

According to the Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations [36] and the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines [35], in cases of grade 1 liver toxicity, ICI treatment can be continued but with careful blood monitoring (AST, ALT, total bilirubin) 1-2 times/week. No specific treatment is recommended in this stage apart from supportive care for symptomatic control.

ICI treatment should be temporarily discontinued if grade 2 or 3 liver toxicity, but permanently withdrawn if grade 4. In the case of grade 2 or greater hepatitis, corticosteroids should be initiated if the abnormal liver tests persist or worsen with significant clinical symptoms in 3 to 5 days. The recommended dose is 0.5-1.0 mg/kg/day prednisone or equivalent, 1-2 mg/kg/d methylprednisolone or equivalent, and 2 mg/kg/d methylprednisolone equivalents if grade 2, 3 and 4 hepatitis, respectively. Steroids should be tapered over 6-8 weeks. ICI treatment can be resumed (if grade 2/3 hepatitis) when liver parameters improve to grade 1 or normal values while on prednisone ≤ 10 mg/day (or equivalent).

In patients with hepatitis refractory to corticosteroids or no responsiveness after three days of continuous administration, a second immunosuppressive regimen should be added. According to ASCO guidelines [35], mycophenolate mofetil (MMF) (500 – 1000 mg BID) or azathioprine (1–2 mg/kg) or tacrolimus (targeting blood levels of 8–10 ng/ml or lower in case of an early response) is recommended. The role of infliximab in immune-mediated hepatitis is unclear considering the potential hepatotoxicity associated with infliximab use. Antithymocyte globulin (1.5 mg/kg) for 48 hours has been added to the treatment with MMF and steroids [38] in cases of severe, fulminant hepatitis and has been reported to be effective.

According to recent data [23], not all patients experiencing immune-mediated hepatitis following treatment with ICI need corticosteroids. More specifically, 16 out of 536 patients treated with anti-PD-1/PD-L1 or CTLA-4 immunotherapy developed histologically proven immune-mediated hepatitis. The decision to start steroids was based on biological (bilirubin >2.5 mg/dl and/or international normalized ratio [INR] >1.5) and/or histological criteria for severity assessment. Overall, six patients presented spontaneous resolution of hepatitis without receiving any corticosteroid treatment. Furthermore, in three of these patients, ICI treatment was re-introduced without recurrence of liver toxicity. The abovementioned indicate again that further investigation is needed regarding severity stratification and accordingly, treatment management in patients presenting with liver irAEs.

CONCLUSIONS

Despite the breakthrough in the management of advanced solid tumors after the introduction of checkpoint inhibitors, a variety of immune-mediated toxicities have emerged. These can be occasionally severe; thus, physicians should be aware of these entities in order to identify them early and to treat them appropriately. Liver irAEs are rare; however, their incidence increases substantially following combination treatment with ICIs. There is a knowledge gap regarding the pathophysiology of these toxicities and the specific risk factors for these adverse events, if any, are not yet elucidated. Better algorithms to identify patients in need for initiation of steroids are needed as well as prognostic indicators for treatment response and recurrence. The diagnosis of liver irAEs is problematic and research should be guided towards the identification of specific biomarkers and/or diagnostic tools to assist with the differential diagnosis of immune-mediated hepatitis. Lastly, the grade classification system should be reviewed and revised to better stratify the grade of severity from a hepatologist's perspective.

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REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252–64.
2. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382(20):1894–905.
3. Hodi FS, O'Day SJ, McDermott DF, Weber WR, Sosman JA, Haanenet JB, al. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl J Med 2010;363(8):711–23.
4. Adachi K, Tamada, K. Immune checkpoint blockade opens

an avenue of cancer immunotherapy with a potent clinical efficacy. Cancer Sci 2015;106(8):945–50.
5. Okoye IS, Houghton M, Tyrrell L, Barakat K, Elahi S. Coinhibitory receptor expression and immune checkpoint blockade: maintaining a balance in CD8(+) T cell responses to chronic viral infections and cancer. Front Immunol 2017;8:1215.
6. Samaan MA, Pavlidis P, Papa S, Powell N, Irving PM. Gastrointestinal toxicity of immune checkpoint inhibitors: from mechanisms to management. Nat Rev Gastroenterol Hepatol 2018;15(4):222-34.
7. Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. Transl Lung Cancer Res 2015;4(5):560–75.
8. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015;13:211.
9. Maughan BL, Bailey E, Gill DM, Agarwal N. Incidence of Immune-Related Adverse Events with Program Death Receptor-1- and Program Death Receptor-1 Ligand-Directed Therapies in Genitourinary Cancers. Front Oncol 2017;7:56.
10. Xu C, Chen YP, Du XJ, Liu JQ, Huang CL, Chen L, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network metaanalysis. BMJ 2018;363:k4226.
11. Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS, MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119(9):1675-682.
12. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget 2017;8(5):8910-20.
13. Bourke JM, O'Sullivan M, Khattak MA. Management of adverse events related to new cancer immunotherapy (immune checkpoint inhibitors). Med J Aust 2016;205(9):418-24.
14. Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belan CP, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. Cancer 2018;124(2):271-7.
15. Xing P, Zhang F, Wang G, Xu Y, Li C, Wang S, et al. Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+IPI: a systematic review and meta-analysis. J Immunother Cancer 2019;7(1):341.
16. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients with Advanced Melanoma. J Clin Oncol 2017;35(7):785-92.
17. Dougan M. Gastrointestinal and Hepatic Complications of Immunotherapy: Current Management and Future Perspectives. Curr Gastroenterol Rep 2020;22(4):15.
18. Shivaji UN, Jeffery L, Gui X, Smith SCL, Ahmad OF, Akbar A, et al. Immune checkpoint inhibitor-associated gastrointestinal and hepatic adverse events and their management. Therap Adv Gastroenterol 2019;12:1756284819884196.
19. De Martin E, Michot JM, Rosmorduc O, Guettier C, Samuel D. Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep 2020;2(6):100170.
20. Parakh S, Cebon J, Klein O. Delayed autoimmune toxicity occurring several months after cessation of anti-PD-1 therapy. Oncologist 2018;23(7):849–51.
21. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
22. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol 2019;70(6):1222-261.
23. De Martin E, Michot J-M, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68(6):1181–90.
24. Riveiro-Barciela M, Barreira-Díaz A, Vidal-González J, Muñoz-Couselo E, Martínez-Valle F, Viladomiu L, et al. Immune-related hepatitis related to checkpoint inhibitors: clinical and prognostic factors. Liver Int 2020; 40(8):1906-16.
25. Huffman BM, Kottschade LA, Kamath PS, Markovic SN. Hepatotoxicity after immune checkpoint inhibitor therapy in melanoma: natural progression and management. Am J Clin Oncol 2018;41(8):760–5.
26. Cheung V, Gupta T, Payne M, Middleton MR, Collier JD, Simmons A, et al. Immunotherapy-related hepatitis: real-world experience from a tertiary centre. Frontline Gastroenterol 2019;10(4):364–71.
27. Wang DY, Salem J-E, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721–8.
28. Johncilla M, Misdraji J, Pratt DS, Agoston AT, Lauwers GY, Srivastava A, et al. Ipilimumab-associated hepatitis: clinicopathologic characterization in a series of 11 cases. Am J Surg Pathol 2015;39(8):1075–84.
29. Papouin B, Mussini C, De Martin E, Guettier C. Hepatic and digestive adverse events of immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1/PD-L1): a clinico-pathological review. Ann Pathol 2018;38(6):338–51.
30. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnelet F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 2016;27(4):559–74.
31. Belli C, Zuin M, Mazzarella L, Trapani D, D'Amico P, Guerini-Rocco E, et al. Liver toxicity in the era of immune checkpoint inhibitors: A practical approach. Crit Rev Oncol Hematol 2018;132:125-9.
32. Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig Dis Sci 2012;57(8):2233–40.
33. Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases in comparison

with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol 2018;31(6):965–73.
34. Fessas P, Possamai LA, Clark J, Daniels E, Gudd C, Mullish BH, et al. Immunotoxicity from checkpoint inhibitor therapy: clinical features and underlying mechanisms. Immunology 2020;159(2):167-77.
35. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol2018;36(17):1714-68.
36. Dougan M, Blidner AG, Choi J, Cooksley T, Glezerman I, Ginex P, et al. Multinational Association of Supportive Care in Cancer (MASCC) 2020 clinical practice recommendations for the management of severe gastrointestinal and hepatic toxicities from checkpoint inhibitors. Support Care Cancer 2020;28(12):6129-43.
37. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv119–42.
38. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016;13(8):473-86.

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