Immune-Mediated Hepatitis during Immunotherapy in Patients with Cancer

Subjects: Oncology
Contributor: Angioletta Lasagna , Paolo Sacchi

Immune-mediated hepatotoxicity (IMH) is not-so-rare complication during treatment with immune checkpoint inhibitors (ICIs). The majority of cases of IMH are asymptomatic and only a few patients may have clinical conditions. The severity of IMH is usually stratified according to Common Terminology for Clinical Adverse Events (CTCAE) criteria, but these scores may overestimate the clinical severity of IMH compared to the Drug-Induced Liver Injury Network (DILIN) scale. The differential diagnosis of IMH is challenging because the elevated liver enzymes can be due to a number of etiologies such as viral infection, autoimmune and metabolic diseases, liver metastases, biliary diseases, and other drugs. The cornerstones of IMH management are represented by withholding or delaying ICI administration and starting immunosuppressive therapy.

hepatitis | immune checkpoint inhibitors | immune-related adverse events (irAEs) | CD8+ T cells | NAFLD | drug-induced liver injury (DILI)

1. Diagnosis

1.1. Clinical Presentation

The majority of immune-mediated hepatotoxicits (IMHs) are asymptomatic and only a few patients may have clinical conditions such as fatigue, abdominal discomfort, fever, rash, and jaundice [1]. Fever is more prevalent in IMHs induced by anti-CTLA-4 inhibitors [2]. The liver imaging in mild to moderate IMH is usually normal, while mild portal lymphadenopathy, periportal edema, and hepatomegaly may be seen in severe IMH [3]. The severity of IMH is usually stratified according to the Common Terminology for Clinical Adverse Events (CTCAE) criteria, but these scores may overestimate the clinical severity of IMH compared to the Drug-Induced Liver Injury Network (DILIN) criteria [4].

The classification of the severity of liver damage should be considered beyond ALT elevation, as should the impairment of the International Normalized Ratio as occurs in the DILIN system which also considers symptoms and other organ failure indexes [5]. However, researchers do not have an explicit criterion for IMH grading different from elevated liver function tests and researchers do not know which of them is more useful in predicting the prognosis of IMH. (**Table 1**).

Table 1. Grading assessment of immune-mediated hepatitis according to the Common Terminology Criteria of Adverse Events (CTCAE) and Drug-Induced Liver Injury Network (DILIN) criteria.

DILIN	CTCAE	Grade
Elevated serum ALT and/or ALP; TBil < 2.5 mg/dL; INR < 1.5; with or without symptoms (fatigue, weakness, nausea, anorexia, right upper abdominal pain, jaundice, pruritus, rash, or weight loss)	ALT/AST < 3× ULN; ALP/GGT > 1–2.5× ULN; TBili < 1.5× ULN	1
Elevated serum ALT and/or ALP; TBil ≥ 2.5 mg/dL or INR ≥ 1.5 without elevated TBil; symptoms may be aggravated	AST/ALT 3–5× ULN; ALP/GGT > 2.5–5× ULN; TBili 2–3× ULN	2
Elevated serum ALT and/or ALP; TBil ≥ 5 mg/dL with or without INR ≥ 1.5; symptoms are further aggravated; indication for hospitalization or prolonged hospitalization	AST/ALT 5–20× ULN; ALP/GGT > 5–20× ULN; TBili > 3× ULN	3
Elevated serum ALT and/or ALP; TBil ≥ 10 mg/dL or daily elevation ≥ 1.0 mg/dL; INR ≥ 1.5 with ascites, encephalopathy, or other organ dysfunction	AST/ALT > 20× ULN; ALP/GGT > 20× ULN; TBili > 10× ULN	4
Death	Death due to hepatoto×icity	5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBil, total bilirubin; INR, international normalized ratio; ULN, upper limit of normal.

The differential diagnosis of IMH is challenging because the elevated liver enzymes can be due to many etiologies such as viral infection, autoimmune and metabolic diseases, liver metastases, biliary diseases, and other drugs. Therefore, it is mandatory to rule out the other causes of liver injury [6].

Firstly, researchers should exclude hepatic virus infection such as HAV, HBV, HCV, HEV CMV, EBV, and HSV using the related bioumoral tests (anti-HAV IgM, HBsAg, anti-HBc IgG, anti-HBc IgM, HBV DNA, anti-HCV, HCV RNA, anti-HEV IgG, anti-HEV IgM, HEV RNA, anti-CMV IgM, CMV DNA, anti-EBV IgM, EBV DNA, anti-HSV IgM, and HSV DNA). The research of anti-tissue antibodies (ANA, ASMA, anti-LKM-1, anti-LC-1, anti-SLA/LP, pANCA, and serum IgG, IgM, IgA) is recommended to rule out autoimmune diseases.

The differential diagnosis between ICI-induced hepatitis and drug-induced autoimmune liver disease is particularly challenging because there are at least seven phenotypes of this form.

The first one, AIH with DILI occurs in patients with known quiescent AIH, and the drug acts as a trigger of the autoimmune liver disorder. In this case, histology may show advanced fibrosis. The second is drug-induced—AIH that affects patients with a low-grade misdiagnosed disease where a drug produces an immune reaction leading to a chronic process and permanent need for immunosuppressive therapy. Other less common forms are IM-DILI, due to autoimmune hypersensitivity frequently presenting with systemic symptoms, indistinguishable from true AIH and responding to IS treatment, mixed autoimmune type, often associated with other autoimmune disorders, and DILI-positive autoantibodies.

Hepatic imaging (ultrasonography, CT scan, and MRI) can be useful to exclude the progression of cancer. The medication history can help to evaluate chemotherapeutic drugs that may also cause liver injury (dacarbazine,

carboplatin, and complementary and herbal medication, or alcohol abuse). NAFLD is due to lipid accumulation in liver cells and tissue inflammation with cytokine release [7]. It can be a potential risk factor for IMH but also a differential diagnosis [8].

Finally, myocarditis, myositis, Wilson's disease, and bone metastasis have to be excluded [9].

1.3. Histological Diagnosis

IMH is typically a clinical diagnosis and a liver biopsy is required only in the case of absence of response to steroids. The pathological features of IMH are scarce. There are clinicopathologic features that support the idea that IMH is a distinct entity from autoimmune hepatitis. IMH rarely presents autoantibodies and/or IgG elevations and the histological patterns are different from those seen in classical autoimmune hepatitis. The typical patterns include acute hepatitis with spotty or confluent necrosis in the centrilobular zone, and granulomatous hepatitis [10] [11]. There may be acute hepatitis with lobular inflammation and acidophil bodies [12]. Lobular hepatitis has the same features as autoimmune hepatitis and with patterns of zone 3 panlobular inflammation. IMH inflammatory infiltrate differs from that of autoimmune hepatitis because it is predominantly composed of activated CD3+ and CD8+ T lymphocytes while CD20+ and CD4+ are characteristic of autoimmune forms [12][13]. In IMH caused by anti-CTLA-4, a pattern of granulomatous hepatitis, with fibrin-ring granulomas and central-vein endothelitis is found [2]. Mild portal fibrosis seems to suggest a trend of acute hepatitis towards chronicity [2].

The guidelines of the European Society of Medical Oncology recommend liver biopsy for patients with IMH and poor or slow response to steroids [14]. Liver biopsy may be useful in different settings:

- To exclude pre-existing diseases;
- To confirm the presence of a pattern consistent with liver injury in the case of ring granulomas and/or endothelitis observed in patients treated with anti-CTLA-4;
- To look for the distinctive picture of liver toxicity related to anti-PD-1/PD-L1 and anti-CTLA4;
- To estimate the degree of liver injury;
- To distinguish IMH from AIH with an atypical clinical pattern;
- To assess a possible evolution to a chronic form of liver damage;
- Liver biopsy has also several limitations, such as cost and the possibility of adverse events, thus should be considered only if it may change the management of patients.

Li and colleagues conducted a retrospective analysis of liver biopsy in a cohort of 213 patients who developed IMH. Patients with ICI hepatitis undergoing a liver biopsy showed longer median (IQR) time to ALT normalization

(42 [1][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24] vs. 33 [1][3][15][16][17][18][19][25][26][27][28][29] days; p = 0.01) and to ALT levels of 100 U/L or less (21 [30][31][32][33][34][35][36][37][38][39] vs. 15 [31][40][41][42] days; p = 0.01). These data underline that performing a liver biopsy in this setting may delay the initiation of corticosteroids and in the resolution of liver inflammation [20].

Parlati et al. conducted a retrospective monocenter study to explore the impact of liver biopsy on the clinical management of IMH. The time for normalization of transaminases was 49 days in those patients who did not undergo liver biopsy and 60 days in the group of patients who did (p = 0.205) [21].

2. Management

2.1. General Recommendations

IMH is caused by an excessive immune response against liver tissue. Therefore, the cornerstones of IMH management are represented by withholding or delaying ICI administration and starting immunosuppressive therapy [22]. A multidisciplinary team, including oncologists, hepatologists, internists, and emergency medicine physicians, is essential for the management of IMH. The international guidelines recommend specialist gastroenterology/hepatology consultation in patients with high-grade IMH. The European Association for the Study of the Liver (EASL) suggests that a multidisciplinary team with a hepatologist should manage all “sufficiently severe” IMHs [23]. Patients with ICI-related hepatitis should be managed by a team including a hepatologist as suggested by the American Gastroenterological Association (AGA) [24], ASCO [43], and ESMO [14], and, above all, in cases of grade ≥ 3 liver enzyme elevation (AGA and high-grade hepatitis (ASCO)) ESMO suggests to refer to hepatologists only if the patient did not respond to a second line immunosuppressive agent.

Li and colleagues reported that early gastroenterology/hepatology consultation in patients with steroid-refractory disease was associated with faster ALT normalization (hazard ratio [HR], 1.89; 95% CI, 1.12–3.19; p = 5.017) and ALT improvement to ≤100 U/L (HR, 1.72; 95% CI, 1.04–2.84; p = 5.034). This beneficial effect was not evident in patients with steroid-responsive hepatitis (HR, 1.12; 95%, 0.83–1.51; p = 5.453) [44].

2.2. When to Start Corticosteroids?

Patients with any degree of ALT elevation should be screened with a full workup for other causes of viral involvement. Once ruled out other causes of liver diseases, management is according to the CTCAE (**Table 1**).

Grade 1 hepatitis can be managed with close monitoring of liver-associated enzymes while the patient continues ICIs. The Society for Immunotherapy of Cancer (SITC) recommends testing liver enzymes [45], while ASCO suggests checking liver enzymes twice a week [43].

Grade 2 hepatitis requires the withdrawal of ICIs. Liver enzymes should be monitored closely until they return to grade 1 level or normalize completely and if there is no improvement and/or increase upon repeat testing, oral corticosteroids (starting at 0.5–1 mg/kg/day of prednisone or an equivalent corticosteroid) can be given [14][43][45].

ICIs can be resumed once improvement is noticed, and corticosteroid reduction should occur slowly over time (4–12 weeks).

Grade 3 hepatitis imposes the permanent discontinuation of ICIs. Treatment with corticosteroids at higher doses (1–2 mg/kg/day (methyl)prednisolone) is recommended. If no improvement is seen in 3 days, physicians should consider adding a secondary agent such as mycophenolate mofetil [14][43][45].

Grade 4 hepatitis imposes the permanent discontinuation of ICIs with the start of corticosteroids at higher doses IV (2 mg/kg/day methylprednisolone) and the possibility of hospitalization. Intravenous steroids should be switched to an oral schedule and weaned in 4 weeks once ALT improves to grade 2 or less [14]. (**Table 1**).

Table 1. Management algorithm for IMH.

Continue ICI; Check LT 1–2 Times Week	Grade 1
Hold ICI; check LT every 3 days; consider liver biopsy; if no improvement start steroid therapy (0.5–1 mg/kg/day of prednisone)	Grade 2
Hold ICI; check LT every 2 days; consider liver biopsy; if no improvement start steroid therapy (1–2 mg/kg/day of prednisone)	Grade 3
Hold ICI; check LT every 1 day; consider liver biopsy; if no improvement start steroid therapy (2 mg/kg/day of prednisone)	Grade 4

ICI: immune checkpoint inhibitors; LT: liver test.

If patients have to receive high-dose steroids for four weeks or longer, they are at risk of opportunistic infections (i.e., *Pneumocystis jiroveci*) and/or reactivation of chronic hepatitis B, so the expert panel agrees on the need to initiate prophylaxis [14][43]. To reduce the risk of infection, budesonide, a drug with 90% hepatic clearance and metabolism, may be evaluated in the case of IMH without liver failure. This type of corticosteroid has fewer side effects and could be maintained in the event of a resumption of ICIs to limit the recurrence of hepatitis and there is no need for dose tapering in order to reinitiate immunotherapy [46][47].

2.3. Refractory IMH to Steroid

Infliximab, a mouse–human chimeric monoclonal antibody anti-TNFα, should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity [41]. If there is no improvement after high-dose steroids, a second immunomodulating agent (i.e., mycophenolate mofetil at the dosage of 500–1000 mg twice daily [2]; azathioprine 1–2 mg/kg/day [48], or tacrolimus with blood levels 8–10 ng/mL [49]) should be considered. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend azathioprine as the first choice in case IMH is refractory to steroids, and mycophenolate mofetil in the case of a failure to respond to azathioprine [50]. No data demonstrate that azathioprine is superior to azathioprine in this setting [51]. Tacrolimus is a calcineurin inhibitor and can be used as a third-line option in patients not improving with mycophenolate mofetil [52]. Recently, plasma exchange has been used in patients with IMH non-responsive to steroids. Riveiro-Barciela and colleagues have

reported clinical success in a woman after the failure of steroids and mycophenolate mofetil [53]. Tocilizumab is an anti-interleukin-6 and has been demonstrated to induce clinical improvement with just a single dose [54].

2.4. When to Rechallenge?

Current guidelines recommend permanent discontinuation of ICIs in the case of grade 4 IMH [14][43]. Several retrospective and few prospective studies described the risk of recurrence of irAEs after rechallenge. The rechallenge with ICIs may depend on the indication, the efficacy of the causative drug, the alternative therapeutic options, and the type and severity of IMH. There are three scenarios:

(i) A class switch scenario from anti-PD-(L)1 to anti-CTLA-4 therapy or vice versa;

(ii) A rechallenge scenario with reintroduction of the same molecule after resolution of IMH;

(iii) A rechallenge scenario with the reintroduction of the same molecule concomitantly with immunosuppressive therapy.

A multicenter, retrospective cohort study at the Dana-Farber/Brigham and Women's Cancer Center and the Massachusetts General Hospital Cancer Center evaluated the hepatitis recurrence after rechallenge. Of the 31 patients who resumed ICI therapy after IMH, six patients (19.4%) developed a new irAE. In particular, 4 patients (12.9%) developed recurrent IMH, 1 patient (3.2%) developed grade 2 pneumonitis, and 1 patient (3.2%) developed grade 3 hypophysitis [55].

Simonaggio and colleagues evaluated the safety of the rechallenge with anti-PD-1 or anti-PD-L1 after an irAE (17 patients have had hepatitis grades 2 to 4 [18%]). Three patients reported the same irAE after rechallenge, but the second irAE was not more severe than the initial IMH [56]. Pollack et al. described 29 patients with IMH (19 with ≥grade 3). Five of these 29 patients (17%) developed an irAE of ≥grade 3 after resuming therapy with anti-PD-1 [57].

The risk of liver injury after rechallenge depends on the class of ICIs. The reintroduction of an anti-CTLA-4 antibody in a patient with previous IMH due to an anti-PD-1 treatment is associated with the development of fulminant hepatitis, while the vice versa does not seem to be true [58].

References

1. Riveiro-Barciela, M.; Barreira-Díaz, A.; Vidal-González, J.; Muñoz-Couselo, E.; Martínez-Valle, F.; Viladomiu, L.; Mínguez, B.; Ortiz-Velez, C.; Castells, L.; Esteban, R.; et al. Immune-related hepatitis related to checkpoint inhibitors: Clinical and prognostic factors. Liver Int. 2020, 40, 1906–1916.

2. De Martin, E.; Michot, J.M.; Papouin, B.; Champiat, S.; Mateus, C.; Lambotte, O.; Roche, B.; Antonini, T.M.; Coilly, A.; Laghouati, S.; et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J. Hepatol. 2018, 68, 1181–1190.
3. Alessandrino, F.; Tirumani, S.H.; Krajewski, K.M.; Shinagare, A.B.; Jagannathan, J.P.; Ramaiya, N.H.; Di Salvo, D.N. Imaging of hepatic toxicity of systemic therapy in a tertiary cancer centre: Chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors. Clin. Radiol. 2017, 72, 521–533.
4. Personeni, N.; Pressiani, T.; D'Alessio, A.; Prete, M.G.; Bozzarelli, S.; Terracciano, L.; Dal Buono, A.; Capogreco, A.; Aghemo, A.; Lleo, A.; et al. Hepatotoxicity in Patients with Hepatocellular Carcinoma on Treatment with Immune Checkpoint Inhibitors. Cancers 2021, 13, 5665.
5. Fontana, R.J.; Watkins, P.B.; Bonkovsky, H.L.; Chalasani, N.; Davern, T.; Serrano, J.; Rochon, J.; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: Rationale, design and conduct. Drug Saf. 2009, 32, 55–68.
6. Shantakumar, S.; Landis, S.; Lawton, A.; Hunt, C.M. Prevalence and incidence of liver enzyme elevations in a pooled oncology clinical trial cohort. Regul. Toxicol. Pharmacol. 2016, 77, 257–262.
7. Day, C.P.; James, O.F. Steatohepatitis: A tale of two "hits"? Gastroenterology 1998, 114, 842–845.
8. Cataldi, M.; Manco, F.; Tarantino, G. Steatosis, Steatohepatitis and Cancer Immunotherapy: An Intricate Story. Int. J. Mol. Sci. 2021, 22, 12947.
9. Touat, M.; Maisonobe, T.; Knauss, S.; Ben Hadj Salem, O.; Hervier, B.; Aure, K.; Szwebel, T.-A.; Kramkimel, N.; Lethrosne, C.; Bruch, J.-F.; et al. Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. Neurology 2018, 91, e985–e994.
10. Kleiner, D.E.; Berman, D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig. Dis. Sci. 2012, 57, 2233–2240.
11. 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, 338–351.
12. Zen, Y.; Yeh, M.M. 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, 965–973.
13. Johncilla, M.; Misdraji, J.; Pratt, D.S.; Agoston, A.T.; Lauwers, G.Y.; Srivastava, A.; Doyle, L.A. Ipilimumab-associated Hepatitis: Clinicopathologic Characterization in a Series of 11 Cases. Am. J. Surg. Pathol. 2015, 39, 1075–1084.

14. Haanen, J.B.A.G.; Carbonnel, F.; Robert, C.; Kerr, K.M.; Peters, S.; Larkin, J.; Jordan, K.; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2017, 28, iv119–iv142.
15. Postow, M.A.; Sidlow, R.; Hellmann, M.D. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N. Engl. J. Med. 2018, 378, 158–168.
16. Polakos, N.K.; Cornejo, J.C.; Murray, D.A.; Wright, K.O.; Treanor, J.J.; Crispe, I.N.; Topham, D.J.; Pierce, R.H. Kupffer cell-dependent hepatitis occurs during influenza infection. Am. J. Pathol. 2006, 168, 1169–1178, quiz 1404-5.
17. Iwama, S.; De Remigis, A.; Callahan, M.K.; Slovin, S.F.; Wolchok, J.D.; Caturegli, P. Pituitary Expression of CTLA-4 Mediates Hypophysitis Secondary to Administration of CTLA-4 Blocking Antibody. Sci. Transl. Med. 2014, 6, 230ra45.
18. Kim, S.T.; Tayar, J.; Trinh, V.A.; Suarez-Almazor, M.; Garcia, S.; Hwu, P.; Johnson, D.H.; Uemura, M.; Diab, A. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: A case series. Ann. Rheum. Dis. 2017, 76, 2061–2064.
19. Faletti, L.; Peintner, L.; Neumann, S.; Sandler, S.; Grabinger, T.; Mac Nelly, S.; Merfort, I.; Huang, C.H.; Tschaharganeh, D.; Kang, T.W.; et al. TNFα sensitizes hepatocytes to FasL-induced apoptosis by NFκB-mediated Fas upregulation. Cell Death Dis. 2018, 9, 909.
20. Li, M.; Sack, J.S.; Bell, P.; Rahma, O.E.; Srivastava, A.; Grover, S.; Zucker, S.D. Utility of Liver Biopsy in Diagnosis and Management of High-grade Immune Checkpoint Inhibitor Hepatitis in Patients with Cancer. JAMA Oncol. 2021, 7, 1711–1714.
21. Parlati, L.; Marcin, K.; Terris, B.; Vallet-Pichard, A.; Corouge, M.; Hollande, C.; Sogni, P.; Mallet, V.; Pol, S. Histological Characteristics and Management of Hepatitis on Immune Checkpoint Inhibitors: A Retrospective Descriptive Study. J. Clin. Med. 2023, 12, 3751.
22. Peeraphatdit, T.B.; Wang, J.; Odenwald, M.A.; Hu, S.; Hart, J.; Charlton, M.R. Hepatotoxicity from Immune Checkpoint Inhibitors: A Systematic Review and Management Recommendation. Hepatology 2020, 72, 315–329.
23. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Drug-induced liver injury. J. Hepatol. 2019, 70, 1222–1261.
24. Dougan, M.; Wang, Y.; Rubio-Tapia, A.; Lim, J.K. AGA Clinical Practice Update on Diagnosis and Management of Immune Checkpoint Inhibitor Colitis and Hepatitis: Expert Review. Gastroenterology 2021, 160, 1384–1393.
25. Wuensch, S.A.; Pierce, R.H.; Crispe, I.N. Local Intrahepatic CD8+ T Cell Activation by a Non-Self-Antigen Results in Full Functional Differentiation. J. Immunol. 2006, 177, 1689–1697.

26. Lalor, P.F.; Sun, P.J.; Weston, C.J.; Martin-Santos, A.; Wakelam, M.J.; Adams, D.H. Activation of vascular adhesion protein-1 on liver endothelium results in an NF-kappaB-dependent increase in lymphocyte adhesion. Hepatology 2007, 45, 465–474.
27. Thomson, A.W.; Knolle, P.A. Antigen-Presenting Cell Function in the Tolerogenic Liver Environment. Nat. Rev. Immunol. 2010, 10, 753–766.
28. Murray, D.A.; Crispe, I.N. TNF-Alpha Controls Intrahepatic T Cell Apoptosis and Peripheral T Cell Numbers. J. Immunol. 2004, 173, 2402–2409.
29. John, B.; Crispe, I.N. Passive and Active Mechanisms Trap Activated CD8+ T Cells in the Liver. J. Immunol. 2004, 172, 5222–5229.
30. Yamamoto, A.; Yano, Y.; Ueda, Y.; Yasutomi, E.; Hatazawa, Y.; Hayashi, H.; Yoshida, R.; Asaji, N.; Shiomi, Y.; Tobimatsu, K.; et al. Clinical features of immune-mediated hepatotoxicity induced by immune checkpoint inhibitors in patients with cancers. J. Cancer Res. Clin. Oncol. 2021, 147, 1747–1756.
31. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Grob, J.J.; Rutkowski, P.; Lao, C.D.; Cowey, C.L.; Schadendorf, D.; Wagstaff, J.; Dummer, R.; et al. Long-Term Outcomes with Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J. Clin. Oncol. 2022, 40, 127–137.
32. Brown, Z.J.; Heinrich, B.; Steinberg, S.M.; Yu, S.J.; Greten, T.F. Safety in treatment of hepatocellular carcinoma with immune checkpoint inhibitors as compared to melanoma and non-small cell lung cancer. J. Immunother. Cancer 2017, 5, 93.
33. Pan, J.; Liu, Y.; Guo, X.; Bai, Z.; Levi Sandri, G.B.; Méndez-Sánchez, N.; Qi, X. Risk factors for immune-mediated hepatotoxicity in patients with cancer treated with immune checkpoint inhibitors: A systematic review and meta-analysis. Expert Opin. Drug Saf. 2022, 21, 1275–1287.
34. Correale, P.; Saladino, R.E.; Giannarelli, D.; Sergi, A.; Mazzei, M.A.; Bianco, G.; Giannicola, R.; Iuliano, E.; Forte, I.M.; Calandruccio, N.D.; et al. HLA Expression Correlates to the Risk of Immune Checkpoint Inhibitor-Induced Pneumonitis. Cells 2020, 9, 1964.
35. Oliveira, L.C.; Porta, G.; Marin, M.L.; Bittencourt, P.L.; Kalil, J.; Goldberg, A.C. Autoimmune hepatitis, HLA and extended haplotypes. Autoimmun. Rev. 2011, 10, 189–193.
36. Sawada, K.; Hayashi, H.; Nakajima, S.; Hasebe, T.; Fujiya, M.; and Okumura, T. Non-alcoholic fatty liver disease is a potential risk factor for liver injury caused by immune checkpoint inhibitor. J. Gastroenterol. Hepatol. 2020, 35, 1042–1048.
37. Mizuno, K.; Ito, T.; Ishigami, M.; Ishizu, Y.; Kuzuya, T.; Honda, T.; Kawashima, H.; Inukai, Y.; Toyoda, H.; Yokota, K.; et al. Real world data of liver injury induced by immune checkpoint inhibitors in Japanese patients with advanced malignancies. J. Gastroenterol. 2020, 55, 653–661.

38. Lasagna, A.; Mascaro, F.; Figini, S.; Basile, S.; Gambini, G.; Klersy, C.; Lenti, M.V.; Di Sabatino, A.; Di Benedetto, A.; Calvi, M.; et al. Impact of proton pump inhibitors on the onset of gastrointestinal immune-related adverse events during immunotherapy. Cancer Med. 2023, 12, 19530–19536.

39. Jenne, C.N.; Kubes, P. Immune surveillance by the liver. Nat. Immunol. 2013, 14, 996–1006.

40. Wang, H.; Yang, H.; Zhou, X.; Zhang, X. Hepatotoxicity Associated with Immune Checkpoint Inhibitors in Clinical Practice: A Study Leveraging Data from the US Food and Drug Administration's Adverse Event Reporting System. Clin. Ther. 2023, 45, 151–159.

41. Wang, W.; Lie, P.; Guo, M.; He, J. Risk of Hepatotoxicity in Cancer Patients Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis of Published Data. Int. J. Cancer 2017, 141, 1018–1028.

42. Liu, Z.; Zhu, Y.; Xie, H.; Zou, Z. Immune-mediated hepatitis induced by immune checkpoint inhibitors: Current updates and future perspectives. Front Pharmacol. 2023, 13, 1077468.

43. Schneider, B.J.; Naidoo, J.; Santomasso, B.D.; Lacchetti, C.; Adkins, S.; Anadkat, M.; Atkins, M.B.; Brassil, K.J.; Caterino, J.M.; Chau, I.; et al. Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J. Clin. Oncol. 2021, 39, 4073–4126.

44. Li, M.; Wong, D.; Sack, J.S.; Vogel, A.S.; Hodi, F.S.; Fong, L.; Lai, J.C.; Grover, S.; Zucker, S.D. Early Liver Specialist Consultation is Associated with Faster Biochemical Resolution of Severe Immune Checkpoint Inhibitor–Induced Hepatitis. J. Natl. Compr. Canc. Netw. 2023, 21, 617–626.e3.

45. Puzanov, I.; Diab, A.; Abdallah, K.; Bingham, C.O., 3rd; Brogdon, C.; Dadu, R.; Hamad, L.; Kim, S.; Lacouture, M.E.; LeBoeuf, N.R.; et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J. Immunother. Cancer 2017, 5, 95.

46. Ziemer, M.; Koukoulioti, E.; Beyer, S.; Simon, J.C.; and Berg, T. Managing Immune Checkpoint-Inhibitor-Induced Severe Autoimmune-like Hepatitis by Liver-Directed Topical Steroids. J. Hepatol. 2017, 66, 657–659.

47. Manns, M.P.; Jaeckel, E.; Taubert, R. Budesonide in Autoimmune Hepatitis: The Right Drug at the Right Time for the Right Patient. Clin. Gastroenterol. Hepatol. 2018, 16, 186–189.

48. Spänkuch, I.; Gassenmaier, M.; Tampouri, I.; Noor, S.; Forschner, A.; Garbe, C.; Amaral, T. Severe hepatitis under combined immunotherapy: Resolution under corticosteroids plus anti-thymocyte immunoglobulins. Eur. J. Cancer 2017, 81, 203–220.

49. Cheung, V.; Gupta, T.; Payne, M.; Middleton, M.R.; Collier, J.D.; Simmons, A.; Klenerman, P.; Brain, O.; Cobbold, J.F. Immunotherapy-related hepatitis: Real-world experience from a tertiary

centre. Frontline Gastroenterol. 2019, 10, 364–371.

50. Mack, C.L.; Adams, D.; Assis, D.N.; Kerkar, N.; Manns, M.P.; Mayo, M.J.; Vierling, J.M.; Alsawas, M.; Murad, M.H.; Czaja, A.J. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American association for the study of liver diseases. Hepatology 2020, 72, 671–722.
51. Cheng, R.; Cooper, A.; Kench, J.; Watson, G.; Bye, W.; McNeil, C.; Shackel, N. Ipilimumab-induced toxicities and the gastroenterologist. J. Gastroenterol. Hepatol. 2015, 30, 657–666.
52. McIlwaine, S.; Cullen, A.; Stratton, L.; Oladipo, B.; Cash, J.; Carser, J.; Braniff, C. The use of tacrolimus in the management of checkpoint inhibitor immunotherapy-induced hepatitis. J. R. Coll. Physicians Edinb. 2022, 52, 20–23.
53. Riveiro-Barciela, M.; Muñoz-Couselo, E.; Fernandez-Sojo, J.; Diaz-Mejia, N.; Parra-López, R.; Buti, M. Acute liver failure due to immune-mediated hepatitis successfully managed with plasma exchange: New settings call for new treatment strategies? J. Hepatol. 2019, 70, 564–566.
54. Stroud, C.R.; Hegde, A.; Cherry, C.; Naqash, A.R.; Sharma, N.; Addepalli, S.; Cherukuri, S.; Parent, T.; Hardin, J.; Walker, P. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J. Oncol. Pharm. Pract. 2019, 25, 551–557.
55. Li, M.; Sack, J.S.; Rahma, O.E.; Hodi, F.S.; Zucker, S.D.; Grover, S. Outcomes After Resumption of Immune Checkpoint Inhibitor Therapy after High-Grade Immune-Mediated Hepatitis. Cancer 2020, 126, 5088–5097.
56. Simonaggio, A.; Michot, J.M.; Voisin, A.L.; Le Pavec, J.; Collins, M.; Lallart, A.; Cengizalp, G.; Vozy, A.; Laparra, A.; Varga, A.; et al. Evaluation of Readministration of Immune Checkpoint Inhibitors after Immune-Related Adverse Events in Patients with Cancer. JAMA Oncol. 2019, 5, 1310–1317.
57. Pollack, M.H.; Betof, A.; Dearden, H.; Rapazzo, K.; Valentine, I.; Brohl, A.S.; Ancell, K.K.; Long, G.V.; Menzies, A.M.; Eroglu, Z.; et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann. Oncol. 2018, 29, 250–255.
58. Delire, B.; De Martin, E.; Meunier, L.; Larrey, D.; Horsmans, Y. Immunotherapy and Gene Therapy: New Challenges in the Diagnosis and Management of Drug-Induced Liver Injury. Front. Pharmacol. 2022, 12, 786174.