Cancer Pathogenesis and Therapy 1 (2023) 46–55

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Review article

Incidence rate and treatment strategy of immune checkpoint inhibitor mediated hepatotoxicity: A systematic review

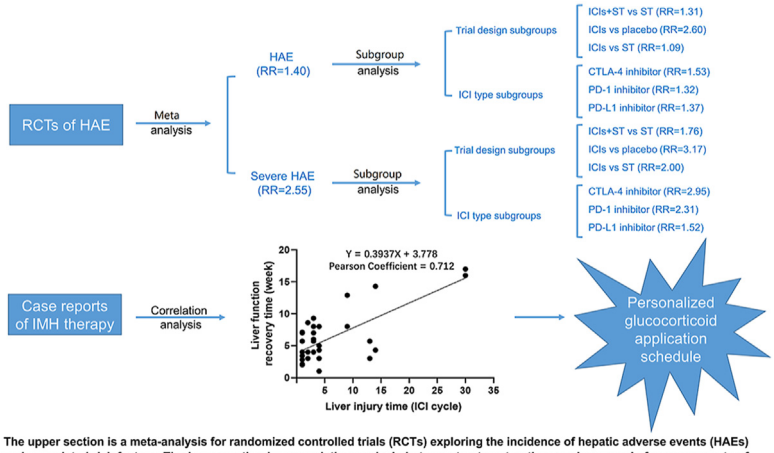
Kang Miao, Li Zhang *

Department of Pulmonary and Critical Care Medicine, Peking Union Medical Collage Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

HIGHLIGHTS

- The hepatic adverse event (HAE) and severe HAE incidence rate following immune checkpoint inhibitor (ICI) administration was 15.3% (1.8–81.8%) and 4.3% (0–40.9%), respectively.
- ICI administration increased the risk of HAE.
- Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors were more likely to be associated with HAE than programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors.
- The total incidence rate of HAE induced by ICIs is similar to that of conventional anti-tumor therapy, but the degree of liver injury tends to be more severe.
- There is a positive correlation between the onset time of Immune-mediated hepatotoxicity and liver injury recovery time.

GRAPHICAL ABSTRACT



The upper section is a meta-analysis for randomized controlled trials (RCTs) exploring the incidence of hepatic adverse events (HAEs) and associated risk factors. The lower section is a correlation analysis between treatment options and prognosis for case reports of severe immune mediated hepatotoxicity (IMH). CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ICI: Immune checkpoint inhibitors; MMF: Mycophenolate mofetil; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; ST: Standard therapy; RR: Risk ratio.

ARTICLE INFO

Keywords:
Immune checkpoint inhibitor
Hepatotoxicity
Treatment strategy
Systematic review

ABSTRACT

Background: A hepatic adverse event (HAE) is defined as a liver injury that occurs following immune checkpoint inhibitor (ICI) administration in oncology Patients. Immune-mediated hepatotoxicity (IMH) is a type of HAE directly caused by ICI and is associated with immune system hyperactivation. HAE incidence varies across different clinical studies. This study aimed to explore the risk factors of HAE and establish a personalized IMH treatment strategy.

Methods: Randomized controlled trials (RCTs) on ICIs and case reports related to IMH were collected and summarized separately. Meta-analysis was performed using Review Manager (version 5.0), whereas correlation analysis and linear regression were performed using SPSS (version 24.0) to evaluate any correlations between the two variables.

Results: Overall, 36 RCTs containing 18,515 patients and 39 case reports met our inclusion criteria. The ICI administration increased the HAE risk (risk ratio [RR] = 1.40) as well as severe HAE (RR = 2.55). The overall HAE incidence and severe incidence were about 15.3% and 4.3%, respectively. Cytotoxic T-lymphocyte-

* Corresponding author. Department of Pulmonary and Critical Care Medicine, Peking Union Medical Collage Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 53 Dongdan North Avenue, Dongcheng District, Beijing 100730, China.
E-mail address: zhanglipumch1026@sina.com (L. Zhang).

https://doi.org/10.1016/j.cpt.2022.11.003
Received 20 September 2022; Received in revised form 12 November 2022; Accepted 23 November 2022

associated protein 4 (CTLA-4) inhibitors have a higher incidence of HAE than programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors. Finally, we found a positive correlation between the onset time of IMH and the recovery time of liver injury.

Conclusions: ICI administration increased the incidence risk of HAE, especially in patients treated with CTLA-4 inhibitors. Regarding IMH treatment, the glucocorticoid dosage must be individually reduced according to the severity and onset time of HAE.

Introduction

Immunotherapy plays an important role in cancer treatment. Activation of immune checkpoints, such as programmed cell death protein receptor-1 (PD-1) or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), can suppress lymphocyte activity,[1] which in turn mediates tumor immune escape.[2] Immune checkpoint inhibitors (ICI) inhibit immune checkpoints and facilitate tumor cell clearance. With the first approval of ipilimumab by the United States Food and Drug Administration (FDA) in 2011 for metastatic melanoma, cancer therapy entered an era of immunotherapy. Subsequently, along with the success of checkmate 037[3] and keynote 001,[4] the PD-1 inhibitors nivolumab and pembrolizumab have been widely used to treat various tumors. ICI exerts anti-tumor efficacy with associated toxicities, which are termed immune-related adverse events (irAEs).[5] Among them, liver toxicity directly mediated by ICI is termed immune-mediated hepatotoxicity (IMH).[6]

By blocking immune checkpoints, ICI activates lymphocytes that kill tumor cells. Immune checkpoints play a crucial role in maintaining immune homeostasis. ICI dysfunction may lead to immune disorders and an excessive immune response.[7] The mechanisms underlying irAEs mainly include off-targeting ICI effects, co-antigens between self-antigens and tumor antigens, antibody-mediated injury, and inflammatory cytokines.[8] Kupffer cells and hepatic sinusoidal endothelial cells can express PD-L1 in the liver, which affects the function of regulatory T-cells (Treg) cells.[9] Similarly, CTLA-4, an inhibitory receptor on the surface of Treg cells, plays an important role in immune tolerance maintenance, and studies have shown that CTLA-4 deficiency induces immune dysregulation syndromes.[10]

Mild IMH may have no notable clinical manifestations that are detectable during routine liver function monitoring. IMH diagnosis relies mainly on liver function tests and the exclusion of other factors that may cause liver damage.[11] IMH severity is generally defined according to the Common Terminology Criteria for Adverse Events (CTCAE), graded by the level of hepatic function, including alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).[12] Transaminase elevations of 1–3-fold, 3–5-fold, 5–20-fold, and 20-fold correspond to grade 1 to 4 liver injury, respectively. Bilirubin elevation is more stringent, with levels corresponding to 1–1.5-fold, 1.5–3-fold, 3–10-fold, and 10-fold. However, ICI is often used with other hepatotoxic drugs; thus, it is difficult to precisely distinguish whether the liver injury was caused by ICI alone. Therefore, liver injury occurring after the administration of ICI is uniformly defined as a hepatic adverse event (HAE).

To date, many large prospective clinical studies regarding ICI for tumor treatment have been reported presenting HAE. However, the studies presented differences, such as the use of different ICI types and co-administered drugs. These variations contribute to the reported incidence rates and relative HAE risk ratios (RR). Hence, we performed a meta-analysis regarding the incidence risk of HAE and conducted a subgroup analysis to explore high-risk factors. In addition, we compiled cases of severe IMH and proposed our own treatment strategies in an effort to provide assistance for future clinical decisions.

Methods

Search strategies

We searched the PubMed, Embase, Web of Science, and Cochrane databases from January 1, 2010, to December 31, 2021. The following search terms were used: “nivolumab” OR “ipilimumab” OR “pembrolizumab” OR “camrelizumab” OR “tislelizumab” OR “cemiplimab” OR “sintilimab” OR “avelumab” OR “durvalumab” OR “atezolizumab” OR “immune checkpoint inhibitor” OR “immune checkpoint blockade” OR “PD-1” OR “PD-L1” OR “CTLA-4”) AND (“Hepatotoxicity” OR “IMH” OR “hepatitis” OR “transaminitis” OR “liver injury” OR “liver damage” OR “hepatic injury” OR “hepatic damage.” Duplicate studies were removed from the retrieved literature and screened manually.

Inclusion criteria

The inclusion criteria for meta-analysis of HAE were as follows: (1) type of study: phase 2 or phase 3 randomized controlled trial (RCT); (2) population: oncology patients; (3) interventions with ICI in the treatment group and without ICI in the control group; and (4) outcome indicators, including specific definitions and detailed data of HAE (liver enzymes or bile acids above the upper limit of normal). The inclusion criteria for IMH case reports were as follows: (1) type of literature: case report and (2) main content of the case report: grade 3 or higher IMH following ICI use.

Exclusion criteria

The exclusion criteria for meta-analysis of HAE were as follows: (1) the outcome did not include specific HAE data or only recorded pathologically confirmed hepatitis and (2) literature quality evaluation: the included literature was screened according to the modified Jadad scale, and low-quality studies with scores of 1–3 were removed. The exclusion criteria for the IMH case report were outcome indicators that did not contain specific treatment methods, courses, or regression.

To ensure the reliability of the screening process and avoid subjective bias, literature screening and methodological quality evaluation were performed and checked independently by two investigators, and any disagreement was further resolved via consultation of a third reviewer.

Data collection

The following data were collected from the HAE meta-analysis: study name, trial phase, first author's name, year of publication, tumor type, ICI type, co-administered medications, total number of patients, number of patients with HAE, and number of patients with severe HAE. In the IMH case report section, collected data included: gender, age, tumor type, ICI type, transaminase levels, total bilirubin levels, IMH onset time, IMH recovery time (time taken from the onset of grade 3 IMH to recovery to grade 1), maximum dose of glucocorticoid, and co-administered medications for IMH.

Statistical analysis

Statistical analyses in the HAE meta-analysis section were performed using Review Manager 5.0 (RevMan 5.0). We calculated the RR of HAE in the ICI group versus that in the control group. Forest plots were also constructed using RevMan 5.0, and the fixed effect model was selected for $I^2 < 50\%$, whereas the random effect model was used for $I^2 \geq 50\%$. Statistical analysis in the case report section was performed using SPSS (version 24.0). Correlation and linear regression analyses were used to explore the correlations between the two variables. R^2 indicated the magnitude of the correlation, with a value closer to 1 indicating a stronger correlation. A *t*-test was then used to verify differences between

the means of two data sets, with $P < 0.05$ representing a statistically significant difference.

Results

Search results

The detailed search strategy is shown in Figure 1. In brief, we searched four databases, including Web of Science, PubMed, Embase, and Cochrane, and found 3937 articles. After excluding duplicates, 1647 articles remained. Finally, 39 case reports[13–49] and 36 RCTs[50–84] containing 18,515 patients were included.

Incidence and hepatic adverse event risk ratio

A total of 36 RCT studies were included in this study. First, we performed a Cochrane risk-of-bias assessment using the methodology of the 36 included articles [Fig. S1]. All the articles used random assignment methods with good data integrity and no selective reporting. Among them, 14 studies achieved allocation protocol concealment, 21 used double-blind trial design protocols, and 18 evaluated efficacy via a central independent review board [Figure 2].

The basic information for each independent study is presented in Table S1. The overall incidence of HAE was 15.3% (1.8–81.8%), of which the incidence was 18.7% (2.1–81.8%) for combination therapy (ICI in combination with standard therapy) and 7.5% (1.8–19.8%) for single ICI therapy. The total incidence of severe hepatotoxicity was 4.3% (0–40.9%), of which the incidence was 6.3% (1.0–40.9%) for combination therapy and 2.4% (0–6.1%) for single ICI therapy.

The pooled RR of the 36 RCTs was 1.40, suggesting that ICI use increased HAE risk [Figure 3]. The funnel plot indicated that seven studies fall outside the 95% confidence interval line, suggesting heterogeneity between the studies [Figure 4A]. Additionally, $I^2 = 68\% > 50\%$ suggested the presence of heterogeneity. Grade 3 or higher liver adverse events were reported in 34 of 36 RCT studies, with a RR of 2.55 [Figure 5]. The funnel plot exhibited an overall fair symmetry, suggesting an insignificant bias [Figure 4B]. Considering the high overall heterogeneity, further subgroup analyses were performed.

First, we conducted a trial design subgroup analysis. The 36 studies were divided into three categories: ICI + ST (standard treatment) *vs.* ST, ICI *vs.* placebo, and ICI *vs.* ST. Patients with ICI were 2.26 (1.22–4.19) times more likely to experience liver injury than those treated with the placebo, which suggested that the liver damage caused by ICI is objective. In the ICI + ST *vs.* ST group, the RR decreased to 1.41 (1.17–1.71), whereas in the ICI *vs.* ST group, there was nearly no difference in the incidence of hepatotoxicity (RR = 1.09 [0.88–1.36]) [Fig. S2]. However, despite subgroup analysis, there was still large heterogeneity, with I^2 reaching 72% in the ICI + ST *vs.* ST group and 80% in the ICI *vs.* placebo group. Therefore, a sensitivity analysis was performed by removing one article at a time. The results showed that in the ICI + ST *vs.* ST group, Robert et al.[51] was the origin of heterogeneity. Unlike other studies, the standard therapy in this study was not traditional chemotherapy; therefore, the incidence rate of hepatotoxicity was significantly lower than that in other groups. After excluding this study, I^2 decreased to 44% with a corrected RR of 1.31. In the ICI vs ST group, Chen et al.[67] was the origin of heterogeneity with a high risk of bias. After excluding this study, I^2 decreased to 64%, with a corrected RR of 2.60 [Fig. S3]. The incidence of severe hepatotoxicity was considerable higher in the experimental group than in the control group in all three subgroups. Furthermore, in the ICI *vs.* ST subgroup, the RR reached 2.00 (1.23–3.27) [Fig. S4]. These results suggested that ICI was the most significant risk factor for severe HAE. In contrast, HAE mediated by ST was predominantly mild. Similarly, Robert et al.[51] introduced substantial heterogeneity into the ICI + ST *vs.* ST subgroup, with I^2 dropping to 51% after exclusion and a corrected RR of 1.76 [Fig. S5].

Second, ICI-type subgroup analysis included CTLA-4, PD-1, and PD-L1 subgroups. The incidence of HAE was slightly higher in the CTLA-4 subgroup than that in the PD-1 and PD-L1 subgroups. The RR of HAE was 1.53 (0.98–2.37) for the CTLA-4 subgroup, 1.32 (1.04–1.67) for the PD-1 subgroup, and 1.37 (1.18–1.58) for the PD-L1 subgroup [Fig. S6]. A comparable trend was observed in severe HAE analysis. The RR was 2.95 (1.03–8.42), 2.31 (1.69–3.15), and 1.52 (1.11–2.08) for the CTLA-4, PD-1, and PD-L1 subgroups, respectively [Fig. S7]. Despite the high I^2 value in the CTLA-4 subgroup, no articles were found with significant heterogeneity. The above results suggest that the incidence of both total and severe HAE was higher with CTLA-4 inhibitors than with PD-1 or PD-L1 inhibitors.

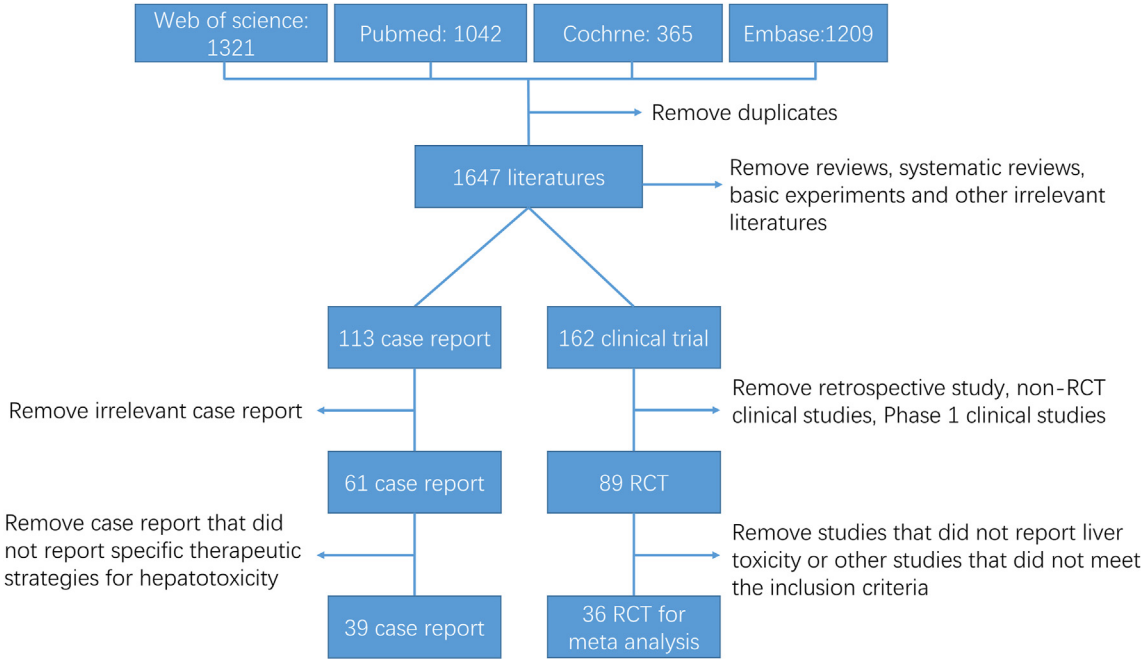


Figure 1. Search process for included literature. RCTs: Randomized controlled trials.

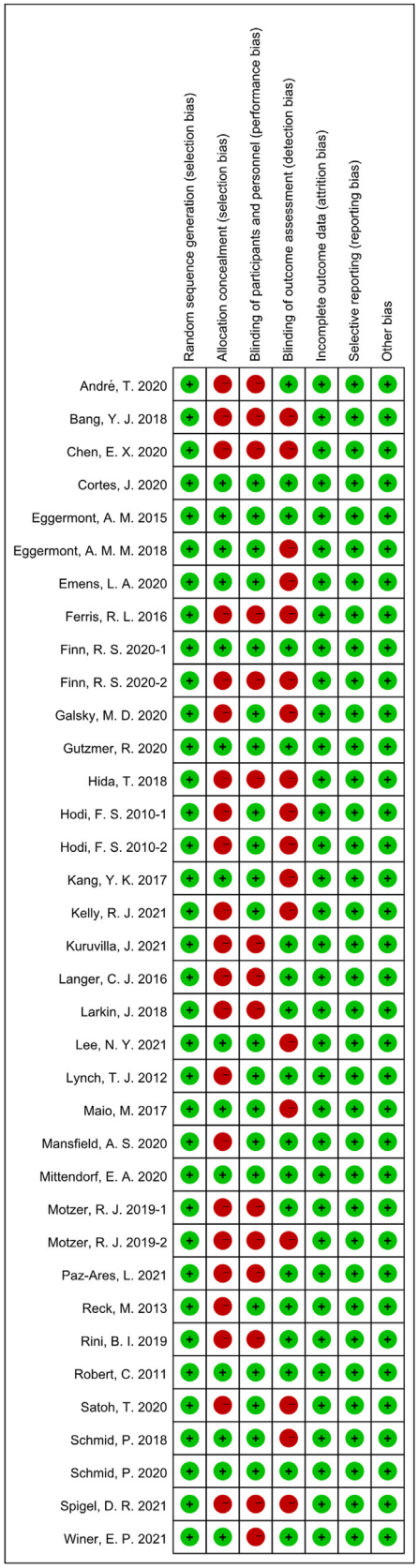


Figure 2. Bias summary risk.

Severe immune-mediated hepatotoxicity

A total of 39 patients with severe IMH (≥grade 3) were included in this study. Among them, 25 were male, and 14 were female, with a median age of 63 years. The cancer types were mainly melanoma (17 cases), lung cancer (13 cases), and kidney cancer (4 cases); other types included malignant glioma, liver cancer, laryngeal cancer, bone giant cell tumor, and bladder cancer. Four patients were treated with a CTLA-4 inhibitor (ipilimumab), 21 with a PD-1 inhibitor (11 pembrolizumab, 10 nivolumab), five with a PD-L1 inhibitor (three atezolizumab, two durvalumab), seven with immune combination therapy (nivolumab combined with ipilimumab), and two with ICI sequential therapy.

Among them, 14 patients presented grade 3 liver injury, of which 10 patients had elevated transaminase levels only, and four patients had combined elevated total bilirubin (TBil). Another 25 patients had grade 4 liver injury, of which nine had elevated transaminase levels only, and 16 had significantly elevated TBil (grade 3/4). Five patients with grade 4 liver injury combined with elevated TBil levels died from acute liver failure [Table S2]. IMH mainly occurred in the 1st–4th ICI treatment cycles (30/39), with only nine patients occurring after the 5th cycle. The average recovery time was 6 weeks, with 5.5 weeks for grade 3 IMH and 6.5 weeks for grade 4 IMH. Correlation analysis revealed a positive correlation between the onset time of IMH and the recovery time (Pearson correlation coefficient = 0.712, $P < 0.001$) [Figure 6A].

Regular-dose glucocorticoid (1–2 mg/kg) was selected for more than 70% of patients, and shock-dose glucocorticoid (0.1 g) was selected for only 10 patients (25.6%). There was no significant correlation between the maximum glucocorticoid dose and the recovery time (Pearson correlation coefficient = 0.189, $P = 0.283$) [Figure 6B]. The average recovery time was 5.5 weeks for patients with a regular dose of glucocorticoids and 7.7 weeks for patients with a shock dose of glucocorticoids ($P = 0.177 > 0.05$) [Figure 6C]. Mycophenolate mofetil (MMF) and ursodeoxycholic acid (UDCA) were the most commonly used glucocorticoids severe IMH treatment. The mean time to recovery of liver function was 5.9 weeks/7.2 weeks in patients with MMF or UDCA and 6.1 weeks/5.5 weeks in patients without MMF or UDCA, with no significant difference ($P_1 = 0.922 > 0.05$; $P_2 = 0.234 > 0.05$) [Figure 6D and E].

Discussion

We performed a statistical meta-analysis on the incidence and risk of HAE. The overall incidence of HAE was approximately 15.3% and the incidence of severe HAE was approximately 4.3%. ICI subgroup analysis revealed that CTLA-4 inhibitors were more likely to develop HAE than PD-1 and PD-L1 inhibitors. There was no significant difference in the overall incidence of HAE between the ICI and ST groups; however, the incidence of severe HAE was 2.0 times higher in the ICI group than in the ST group. This suggests that the total odds of liver injury induced by ICI are comparable to those of conventional anti-tumor therapy; however, the degree of HAE tends to be more severe. Therefore, if mild to moderate HAE occurs in patients undergoing anti-tumor therapy with ICI combined with chemotherapy, IMH should not be considered immediately. Clinicians should consider the chemotherapy-induced liver injury and select an appropriate treatment strategy. In contrast, severe HAE is more likely to be associated with ICI. Thus, severe HAE can be treated as IMH at an early stage following the initial differential diagnosis.

The treatment strategy for severe IMH is based on glucocorticoids with different doses depending on the severity of liver injury. A liver biopsy is usually performed in patients with glucocorticoid-refractory IMH. This can assist the differentiation of IMH from autoimmune disease, liver metastasis, or other diseases that may cause liver dysfunction. In addition, liver biopsy can also help guide typing and specific treatment

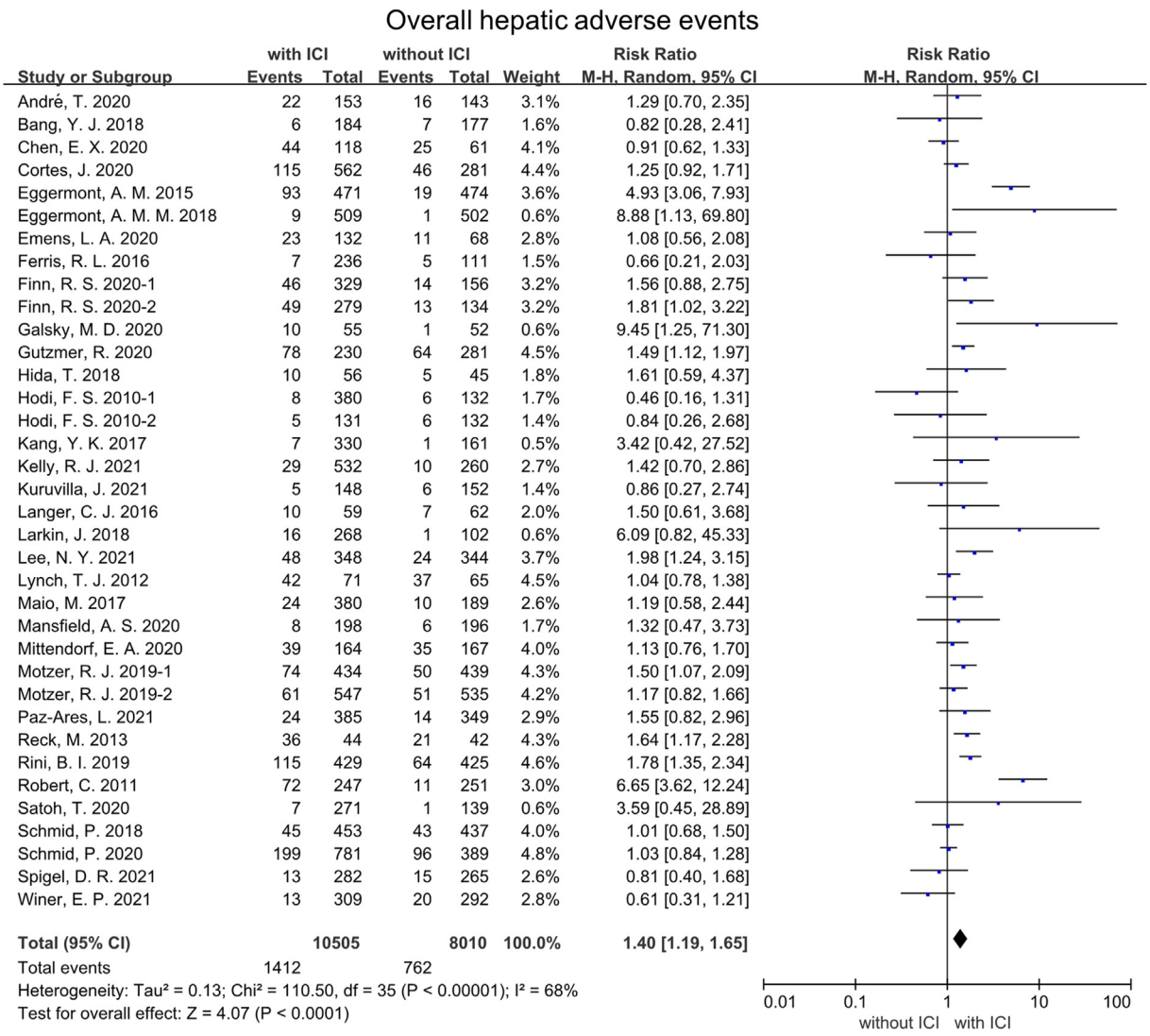


Figure 3. Overall hepatic adverse events forest plot. ICI: Immune checkpoint inhibitors; CI:Confidence interval.

regimens for IMH.[11] According to liver biopsy, IMH can be broadly classified into three types: (1) Hepatocellular injury, which manifests as lobular hepatitis with inflammatory cell infiltration in the center of lobules, accompanied by scattered focal necrosis, eosinophilic vesicles, and granuloma formation. The clinical features are characterized by significantly elevated transaminases with normal or mildly elevated bilirubin levels; (2) bile duct injury type, manifested as bile duct injury with mild portal edema. The clinical features are characterized by elevated bilirubin levels (severe cases may be accompanied by obvious jaundice), with normal or mildly elevated transaminases; and (3) mixed

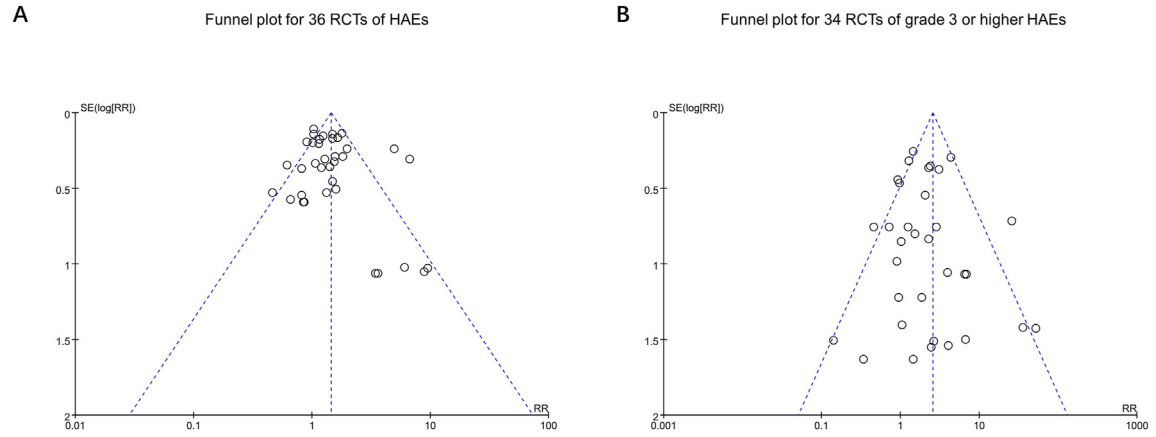


Figure 4. Funnel plot. (A) Funnel plot for 36 RCTs of HAEs; (B) Funnel plot for 34 RCTs of grade 3 or higher HAEs.RCTs: Randomized controlled trials; HAEs: Hepatic adverse events.

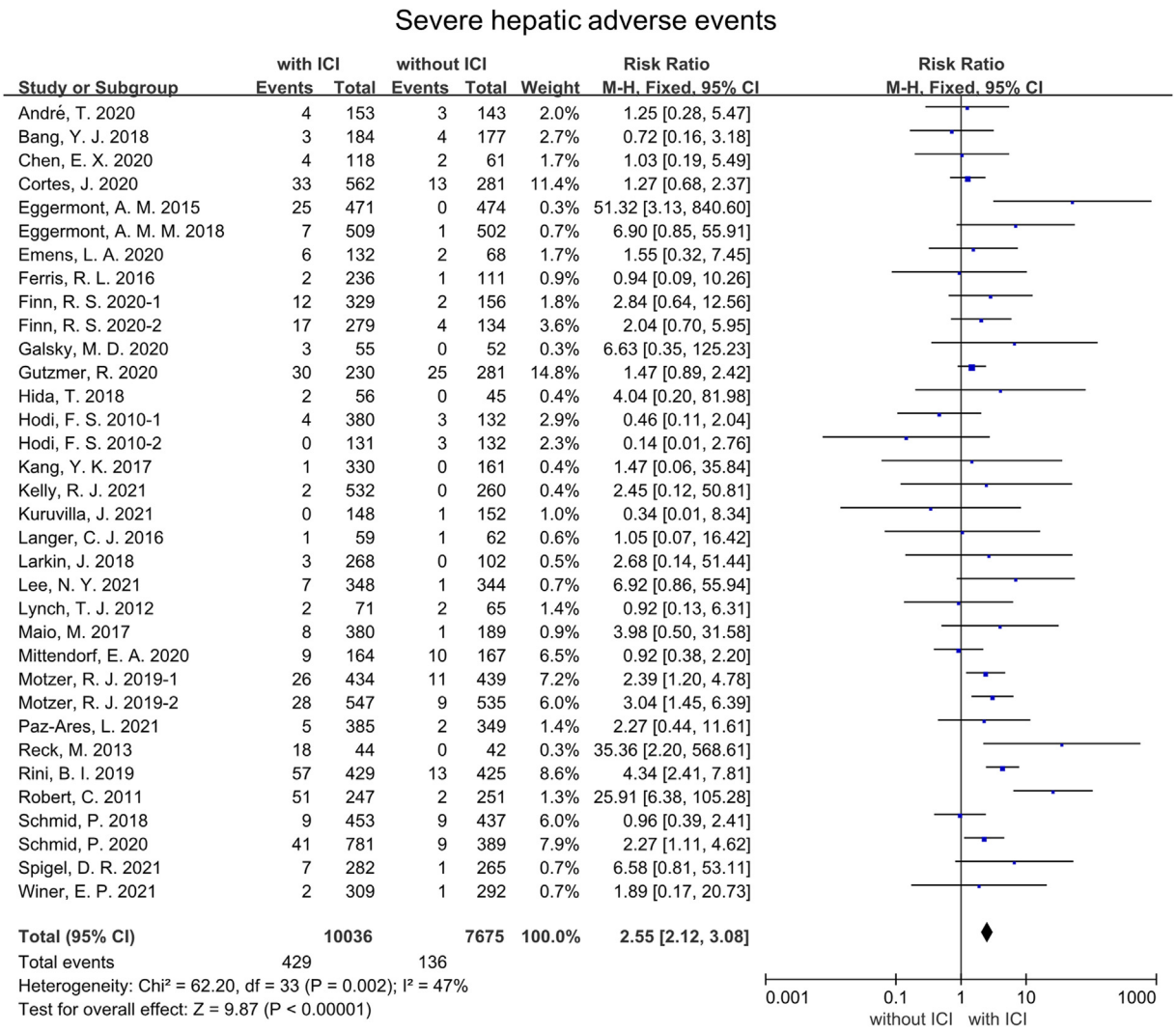


Figure 5. Severe hepatic adverse events forest plot. ICI: Immune checkpoint inhibitors; CI: Confidence interval.

hepatocellular and bile duct injury, characterized by both hepatocellular and bile duct injury, with markedly elevated transaminase and bilirubin.[85] Justine et al. suggested that the pattern of inflammation, degree of lobular damage, presence of granulomas, and endothelialitis did not predict the response to glucocorticoids. Furthermore, Tsung et al. reported that 71.4% of patients with IMH had a cholestatic injury profile at onset and were more likely to receive glucocorticoids (55% *vs.* 12%).[86] Of the 25 patients with grade 4 liver injury in our analysis, 15 had mixed injury (60%), of which five (33.3%) developed liver failure, whereas neither grade 3 nor grade 4 liver injury patients with elevated transaminase levels developed liver failure. This suggests that liver injury with elevated bilirubin levels usually indicates severe tissue damage, which is a high risk for liver failure and requires more aggressive treatment.

The first step in IMH diagnosis was to screen for possible causes of HAE, such as hepatitis virus, opportunistic infections, autoimmune diseases, and liver metastases. Tumor metastasis can be identified by abdominal-enhanced computed tomography.[86] Joana et al. reported that five of eight patients with severe HAE were eventually diagnosed with liver metastasis.[87] In addition, liver metastases can cause acquired immunotherapy resistance via CD8+ T-cell deletion.[88] Autoimmune hepatitis is another common cause of abnormal liver function and shares some features with IMH. However, there were some notable differences between them; autoimmune hepatitis tends to occur in middle-aged women, and laboratory tests usually manifest as significantly elevated serum immunoglobulin (Ig)G (or gamma-globulin) and positive autoantibodies (including antinuclear antibodies, anti-smooth muscle antibodies, anti-liver microsomal type I antibodies, or anti-hepatocyte cytoplasmic type I antibodies).[89] In comparison, the IMH group showed no female predominance. The majority of patients with IMH were negative for anti-smooth muscle antibodies, antinuclear antibodies, and IgG. Half of the IMH patients were positive for antinuclear antibodies; thus, it was not a sufficient marker for distinguishing IMH from autoimmune hepatitis.[90]

In the last section, we present a personal view of IMH therapy and glucocorticoid tapering strategy [Figure 7]. Firstly, elevated bilirubin levels indicated a high likelihood of serious tissue damage.[91] If IMH is accompanied by elevated bilirubin levels, UDCA should be added in time, and IMH should be considered at a higher level. Second, previous algorithms have suggested that grade 2 liver injuries require glucocorticoid therapy. However, we found that immunotherapy combined with chemotherapy was the dominant treatment modality and that mild liver injury was more likely induced by chemotherapy. Therefore, we suggested that glucocorticoid (0.5–1 mg/kg) should only be used for at least grade 3 IMH. Glucocorticoid dosage in patients with grade 4 IMH should be started at 1–2 mg/kg. If no improvement is observed within three days, immunosuppressant MMF could be used in combination[6].

MMF is one of the most widely used agents for IMH other than glucocorticoids. A relationship between MMF and successful glucocorticoid tapering in glucocorticoid-resistant IMH has been reported.[38] Therefore, researchers use it as the first choice of treatment for IMH,

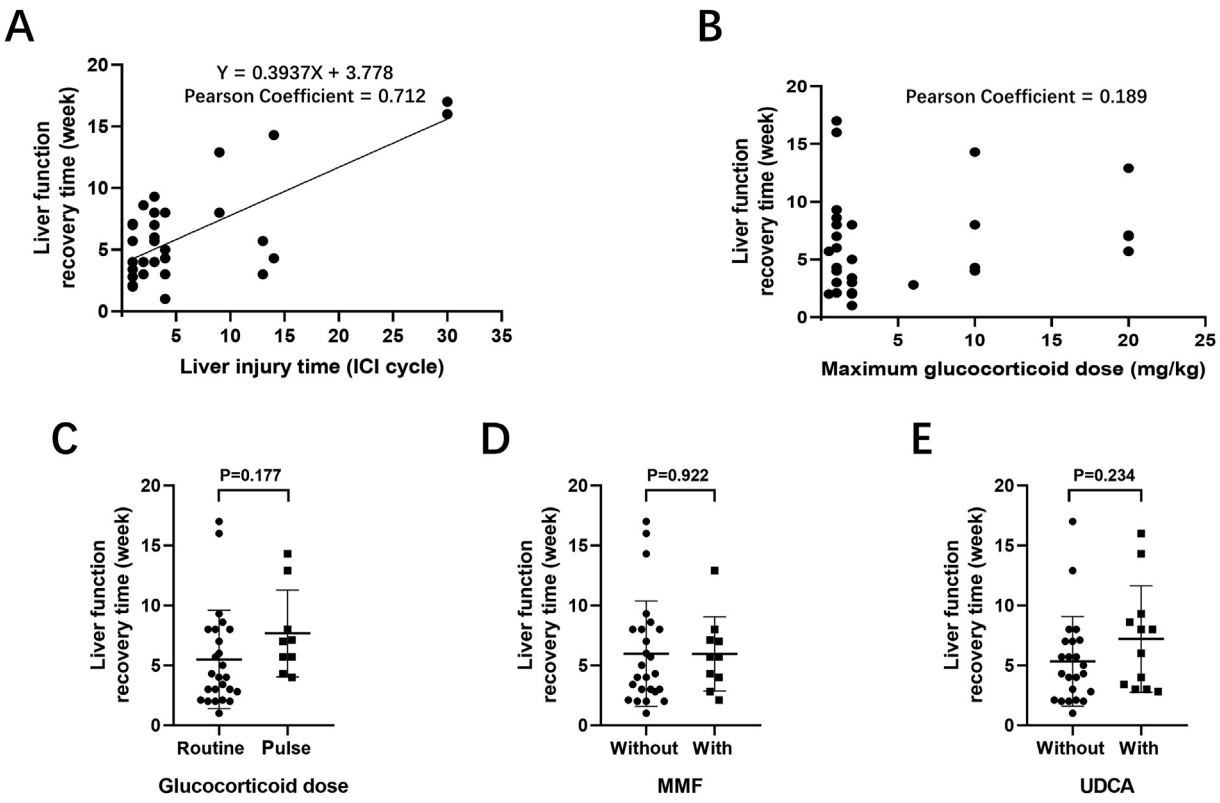


Figure 6. Correlation Analyses. (A) Correlation between liver injury time and liver function recovery time; (B) Correlation between maximum glucocorticoid dose and liver function recovery time; (C) Liver function recovery time: routine dose glucocorticoid vs pulse dose glucocorticoid; (D) MMF effect on liver function recovery time; (E) UDCA effect on liver function recovery time. MMF: Mycophenolate mofetil; UDCA: Ursodesoxycholic acid.

after glucocorticoid therapy. Interleukin (IL)-6 is a multifunctional pro-inflammatory cytokine secreted by lymphocytes and is associated with T-cell activation, immunoglobulin secretion, and acute-phase protein synthesis initiation in the liver.[92] Tocilizumab is an IL-6 monoclonal antibody with a potential therapeutic effect against IMH.[93] However, Serviddio et al. found that tocilizumab caused hepatotoxicity in patients with COVID-19.[94] Therefore, using tocilizumab for patients with IMH should be carefully considered. Infliximab is a biological agent used to treat irAE colitis. Although there was a report of successful treatment of IMH with infliximab,[36] it is not commonly recommended for liver injury patients due to its hepatic damaging effects.[95] Analysis of the correlation between glucocorticoid dose and efficacy revealed that glucocorticoid

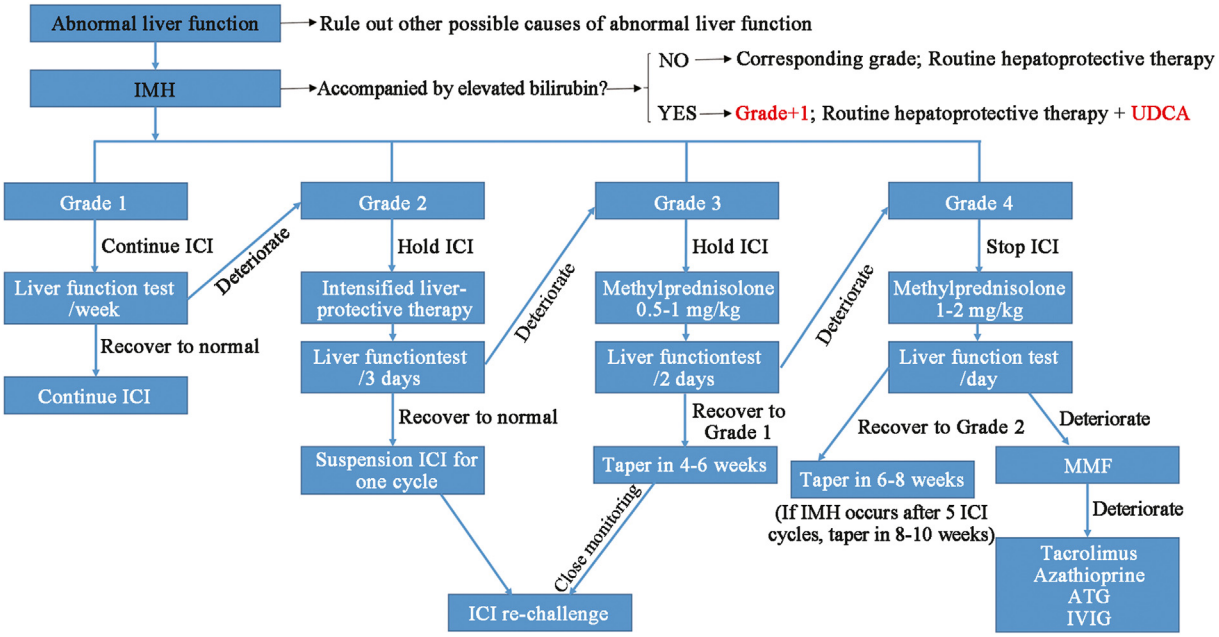


Figure 7. Immune-mediated hepatitis treatment recommendations. IMH: Immune-mediated hepatotoxicity; ICI:Immune checkpoint inhibitor; MMF: Mycophenolate mofetil; UDCA:Ursodesoxycholic acid; ATG:Anti-human thymus globulin; IVIG: Intravenous immunoglobulin.

with shock doses (0.5–1 g) did not show significant efficacy and may induce risk of infection; thus, it is not recommended as a priority. Other drugs that have been reported, but lack large-scale validation, include intravenous immunoglobulin (IVIG), thymocyte globulin, azathioprine, tacrolimus, acetylcysteine, and budesonide.[36]

For patients with grade 4 IMH, the glucocorticoid dosage can be gradually reduced when the liver function recovers to grade 2.[96] However, our correlation analysis showed a positive correlation between the time of liver function recovery and the time of liver injury onset. Therefore, we suggest that the glucocorticoid taper speed could be slowed to 8–10 weeks in patients with severe IMH that occurs after multiple cycles of treatment. It is important to note that long-term glucocorticoid use may cause bone calcium loss and secondary infection; thus, prophylactic anti-infection, calcium, and vitamin D supplements for patients treated with glucocorticoids for >4–6 weeks are necessary.[97]

Conclusion

As tumor therapy entered the immune era, ICI has been widely applied to various cancer types. However, along with the large-scale application of ICI in clinical practice, more types of irAEs are gradually being recognized. The incidence and relative risk of HAE were summarized by our meta-analysis, which provides clinicians with an intuitive understanding of HAE. In addition, previous guidelines provide guidance on the dosage of glucocorticoids, and clinicians could not determine the duration of glucocorticoid application. Therefore, we performed an analysis of the severe IMH reported in case reports and proposed an individualized glucocorticoid reduction strategy that could contribute to improved glucocorticoid management.

Funding

None.

Author contributions

Kang Miao: Study concept and design, acquisition of data, analysis, and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for intellectual content. Li Zhang: administrative, technical, or material support, and study supervision.

Ethics statement

The study was designed in accordance with the ethical guidelines of the *Declaration of Helsinki*.

Data availability statement

This review has not yet been registered. Other data supporting the findings of this study (including the review protocol) are available from the corresponding author upon reasonable request.

Conflicts of interest

None.

Acknowledgment

The authors would like to thank Prof. Bei Tan for the guidance on the clinical application of glucocorticoids and immunosuppressants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2022.11.003.

References

1. Velcheti V, Schalper K. Basic overview of current immunotherapy approaches in cancer. *Am Soc Clin Oncol Educ Book*. 2016;35:298–308. https://doi.org/10.1200/EDBK_156572.
2. Vago L, Gojo I. Immune escape and immunotherapy of acute myeloid leukemia. *J Clin Invest*. 2020;130:1552–1564. https://doi.org/10.1172/jci129204.
3. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375–384. https://doi.org/10.1016/s1470-2045(15)70076-8.
4. Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol*. 2019;30:582–588. https://doi.org/10.1093/annonc/mdz011.
5. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ*. 2018;360:k793. https://doi.org/10.1136/bmj.k793.
6. Peeraphatdit TB, Wang J, Odenwald MA, et al. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. *Hepatology*. 2020;72:315–329. https://doi.org/10.1002/hep.31227.
7. Hussaini S, Chehade R, Boldt RG, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors - a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;92, 102134. https://doi.org/10.1016/j.ctrv.2020.102134.
8. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139–148. https://doi.org/10.1016/j.ejca.2015.11.016.
9. Doherty DG. Immunity, tolerance and autoimmunity in the liver: a comprehensive review. *J Autoimmun*. 2016;66:60–75. https://doi.org/10.1016/j.jaut.2015.08.020.
10. Schubert D, Bode C, Kenefeck R, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat Med*. 2014;20:1410–1416. https://doi.org/10.1038/nm.3746.
11. Jennings JJ, Mandaliya R, Nakshabandi A, et al. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. *Expet Opin Drug Metabol Toxicol*. 2019;15:231–244. https://doi.org/10.1080/17425255.2019.1574744.
12. Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the common terminology criteria for adverse events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr (Engl Ed)*. 2021;112:90–92. https://doi.org/10.1016/j.ad.2019.05.009.
13. Gelsomino F, Vitale G, D'Errico A, et al. Nivolumab-induced cholangitic liver disease: a novel form of serious liver injury. *Ann Oncol*. 2017;28:671–672. https://doi.org/10.1093/annonc/mdw649.
14. Bhave P, Buckle A, Sandhu S, et al. Mortality due to immunotherapy related hepatitis. *J Hepatol*. 2018;69:976–978. https://doi.org/10.1016/j.jhep.2018.06.012.
15. Spänkuch I, Gassenmaier M, Tampouri I, et al. Severe hepatitis under combined immunotherapy: resolution under corticosteroids plus anti-thymocyte immunoglobulins. *Eur J Cancer*. 2017;81:203–205. https://doi.org/10.1016/j.ejca.2017.05.018.
16. Roberts JH, Smylie M, Oswald A. Hepatitis is the new myositis: immune checkpoint inhibitor-induced myositis. *Melanoma Res*. 2018;28:484–485. https://doi.org/10.1097/cmr.0000000000000485.
17. Chmiel KD, Suan D, Liddle C, et al. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. *J Clin Oncol*. 2011;29:e237–e240. https://doi.org/10.1200/jco.2010.32.2206.
18. Kanaoka K, Moriizumi K, Okada H, et al. Pembrolizumab-induced delayed-onset hepatitis. *Case Rep Gastroenterol*. 2020;14:586–592. https://doi.org/10.1159/000509953.
19. Kobayashi K, Nakachi I, Mitsuishi A, et al. Successful retreatment using pembrolizumab for non-small-cell lung cancer after severe immune-related hepatitis: a case report. *Clin Lung Cancer*. 2020;21:e30–e32. https://doi.org/10.1016/j.cllc.2019.02.004.
20. Kubo T, Sugawara T, Shinkawa T, et al. Fatal fulminant hepatitis induced by combined ipilimumab and nivolumab therapy despite favorable histologic response and confirmed by autopsy in a patient with clear cell renal cell carcinoma. *Immunol Med*. 2020;44:136–141. https://doi.org/10.1080/25785826.2020.1788229.
21. Mathew Thomas V, Bindal P, Ann Alexander S, et al. Nivolumab-induced hepatitis: a rare side effect of an immune check point inhibitor. *J Oncol Pharm Pract*. 2020;26:459–461. https://doi.org/10.1177/1078155219837342.
22. Tsukita Y, Miyauchi E, Fukudo M, et al. Immunotherapy-related hepatitis and thrombocytopaenia induced by the very low dose of only 90 mg of atezolizumab. *Eur J Cancer*. 2020;133:22–24. https://doi.org/10.1016/j.ejca.2020.04.008.
23. Yildirim S, Deniz K, Doğan E, et al. Ipilimumab-associated cholestatic hepatitis: a case report and literature review. *Melanoma Res*. 2017;27:380–382. https://doi.org/10.1097/cmr.0000000000000366.
24. Ziemer M, Koukoulioti E, Beyer S, et al. Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids. *J Hepatol*. 2017;66:657–659. https://doi.org/10.1016/j.jhep.2016.11.015.
25. Wu Z, Lai L, Li M, et al. Acute liver failure caused by pembrolizumab in a patient with pulmonary metastatic liver cancer: a case report. *Medicine (Baltim)*. 2017;96, e9431. https://doi.org/10.1097/md.0000000000009431.
26. Ahmed T, Pandey R, Shah B, et al. Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy. *BMJ Case Rep*. 2015;2015, bcr2014208102. https://doi.org/10.1136/bcr-2014-208102.

27. Honma Y, Shibata M, Gohda T, et al. Rapid progression of liver fibrosis induced by acute liver injury due to immune-related adverse events of atezolizumab. *Intern Med*. 2021;60:1847–1853. https://doi.org/10.2169/internalmedicine.6535–20.
28. Inamori O, Miyagawa-Hayashino A, Ueno A, et al. Fulminant hepatitis as an immune-related adverse event after nivolumab treatment. *Pathol Int*. 2019;69:434–436. https://doi.org/10.1111/pin.12812.
29. Kundumadam S, Mohamad B, Muthusamy A, et al. Pembrolizumab-induced immune-mediated hepatitis and concurrent hepatitis B reactivation in a patient with non-small cell lung cancer. *Cureus*. 2020;12, e11522. https://doi.org/10.7759/cureus.11522.
30. Kurokawa K, Hara M, Iwakami SI, et al. Cholestatic liver injury induced by pembrolizumab in a patient with lung adenocarcinoma. *Intern Med*. 2019;58:3283–3287. https://doi.org/10.2169/internalmedicine.2591–18.
31. Liu Y, Zhang J, Yin Z, et al. Compromise or not? A case report of successful treatment of pembrolizumab-induced hepatitis in a patient with non-small cell lung cancer with low-dose methylprednisolone and bicyclol. *Thorac Cancer*. 2020;11:2023–2030. https://doi.org/10.1111/1759-7714.13463.
32. Matsubara T, Nishida T, Higaki Y, et al. Nivolumab induces sustained liver injury in a patient with malignant melanoma. *Intern Med*. 2018;57:1789–1792. https://doi.org/10.2169/internalmedicine.9851-17.
33. McGuire HM, Shklovskaya E, Edwards J, et al. Anti-PD-1-induced high-grade hepatitis associated with corticosteroid-resistant T cells: a case report. *Cancer Immunol Immunother*. 2018;67:563–573. https://doi.org/10.1007/s00262-017-2107-7.
34. Nakamura M, Otsuka T, Hayashi R, et al. Durvalumab-induced immune-related hepatitis in a patient with non-small cell lung cancer. *Intern Med*. 2020;59:2711–2717. https://doi.org/10.2169/internalmedicine.4699–20.
35. Nakano K, Nishizawa M, Fukuda N, et al. Mycophenolate mofetil as a successful treatment of corticosteroid-resistant immune checkpoint inhibitor-induced hepatitis. *Oxf Med Case Reports*. 2020;2020:omaa027. https://doi.org/10.1093/omcr/omaa027.
36. Nakashima K, Demura Y, Oi M, et al. Infliximab was found to be effective for treating immunosuppressive drug-resistant hepatitis due to durvalumab. *Intern Med*. 2020;59:3055–3059. https://doi.org/10.2169/internalmedicine.5216-20.
37. Namiki T, Nojima K, Chikazawa S, et al. Dramatic effect of nivolumab against melanoma and immune-related liver toxicity: a detailed histopathological and immunohistochemical analysis of nivolumab-induced liver toxicity. *J Dermatol*. 2019;46:e182–e183. https://doi.org/10.1111/1346-8138.14710.
38. Omori G, Takada K, Murase K, et al. Successful mycophenolate mofetil treatment of a patient with severe steroid-refractory hepatitis evoked by nivolumab plus ipilimumab treatment for relapsed bladder cancer. *Clin Case Rep*. 2021;9:654–659. https://doi.org/10.1002/ccr3.3597.
39. Sekai I, Hagiwara S, Watanabe T, et al. A case with hepatic immune-related adverse events caused by nivolumab exhibiting impaired accumulation of regulatory T cells. *Clin J Gastroenterol*. 2021;14:1191–1196. https://doi.org/10.1007/s12328-020-01317-y.
40. Simonelli M, Di Tommaso L, Baretti M, et al. Pathological characterization of nivolumab-related liver injury in a patient with glioblastoma. *Immunotherapy*. 2016;8:1363–1369. https://doi.org/10.2217/imt-2016-0057.
41. Sun CY, Shen CI, Feng JY, et al. Severe hepatitis related to immune-checkpoint inhibitor in a patient with non-small-cell lung cancer and pulmonary tuberculosis. *Postgrad Med*. 2021;97:556–557. https://doi.org/10.1136/postgradmedj-2020-138123.
42. Tanaka R, Fujisawa Y, Sae I, et al. Severe hepatitis arising from ipilimumab administration, following melanoma treatment with nivolumab. *Jpn J Clin Oncol*. 2017;47:175–178. https://doi.org/10.1093/jjco/hyw167.
43. Thorsteinsdottir T, Løitegård T, Reims HM, et al. Fatal cholestatic liver injury during treatment with PD1 immune checkpoint inhibitor for malignant melanoma: a case report. *Case Rep Oncol*. 2020;13:659–663. https://doi.org/10.1159/000507695.
44. Dominick A, Mohyuddin GR, Fields-Meehan J, et al. Combination immunotherapy associated with severe hepatotoxicity and fatal aplastic anemia. *Am J Therapeut*. 2020. https://doi.org/10.1097/mjt.0000000000001193.
45. Hashiguchi M, Tamai T, Nakazawa J, et al. Pulse steroid therapy to treat liver injury with risk of liver failure due to immune-related adverse events: a case report. (in Japanese). *Jpn J Gastroenterol*. 2021;118:175–182. https://doi.org/10.11405/nisshoshi.118.175.
46. Kopecký J, Kubecek O, Geryk T, et al. Hepatic injury induced by a single dose of nivolumab - a case report and literature review. *Klin Onkol*. 2019;32:133–138. https://doi.org/10.14735/amko2019133.
47. Kwan JM, Cheng R, Feldman LE. Hepatotoxicity and recurrent NSTEMI while on pembrolizumab for metastatic giant cell bone tumor. *Am J Med Sci*. 2019;357:343–347. https://doi.org/10.1016/j.amjms.2018.11.017.
48. Samara Y, Yu CL, Dasanu CA. Acute autoimmune myocarditis and hepatitis due to ipilimumab monotherapy for malignant melanoma. *J Oncol Pharm Pract*. 2019;25:966–968. https://doi.org/10.1177/1078155218755868.
49. Syed T, Abdullah A, Mubasher M, et al. Nivolumab-induced delayed autoimmune hepatitis-A diagnostic and therapeutic challenge. *Am J Therapeut*. 2020;27:e317–e319. https://doi.org/10.1097/mjt.0000000000000983.
50. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711–723. https://doi.org/10.1056/NEJMoa1003466.
51. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364:2517–2526. https://doi.org/10.1056/NEJMoa1104621.
52. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol*. 2012;30:2046–2054. https://doi.org/10.1200/jco.2011.38.4032.
53. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol*. 2013;24:75–83. https://doi.org/10.1093/annonc/mds213.
54. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16:522–530. https://doi.org/10.1016/s1470-2045(15)70122-1.
55. Ferris RL, Blumenschein Jr G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856–1867. https://doi.org/10.1056/NEJMoa1602252.
56. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497–1508. https://doi.org/10.1016/s1470-2045(16)30498-3.
57. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390:2461–2471. https://doi.org/10.1016/s0140-6736(17)31827-5.
58. Maio M, Scherpereel A, Calabrò L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol*. 2017;18:1261–1273. https://doi.org/10.1016/s1470-2045(17)30446-1.
59. Bang YJ, Ruiz EY, Van Cutsem E, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. *Ann Oncol*. 2018;29:2052–2060. https://doi.org/10.1093/annonc/mdy264.
60. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789–1801. https://doi.org/10.1056/NEJMoa1802357.
61. Hida T, Kaji R, Satouchi M, et al. Atezolizumab in Japanese patients with previously treated advanced non-small-cell lung cancer: a subgroup analysis of the phase 3 OAK study. *Clin Lung Cancer*. 2018;19:e405–e415. https://doi.org/10.1016/j.cllc.2018.01.004.
62. Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. *J Clin Oncol*. 2018;36(1):383–390. https://doi.org/10.1200/jco.2016.71.8023.
63. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced Renar-cell carcinoma. *N Engl J Med*. 2019;380:1103–1115. https://doi.org/10.1056/NEJMoa1816047.
64. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370–1385. https://doi.org/10.1016/s1470-2045(19)30413-9.
65. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116–1127. https://doi.org/10.1056/NEJMoa1816714.
66. André T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383:2207–2218. https://doi.org/10.1056/NEJMoa2017699.
67. Chen EX, Jonker DJ, Loree JM, et al. Effect of combined immune checkpoint inhibition vs best supportive care alone in patients with advanced colorectal cancer: the Canadian Cancer Trials Group CO.26 Study. *JAMA Oncol*. 2020;6:831–838. https://doi.org/10.1001/jamaoncol.2020.0910.
68. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet*. 2020;396:1817–1828. https://doi.org/10.1016/s0140-6736(20)32531-9.
69. Emens LA, Esteva FJ, Beresford M, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. *Lancet Oncol*. 2020;21:1283–1295. https://doi.org/10.1016/s1470-2045(20)30465-4.
70. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–1905. https://doi.org/10.1056/NEJMoa1915745.
71. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 20 2020;38:193–202. https://doi.org/10.1200/jco.19.01307.
72. Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38:1797–1806. https://doi.org/10.1200/jco.19.03091.
73. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395:1835–1844. https://doi.org/10.1016/s0140-6736(20)30934-x.
74. Mansfield AS, Każarnowicz A, Karaseva N, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell

lung cancer (IMpower133): a randomized phase I/III trial. *Ann Oncol*. 2020;31: 310–317. https://doi.org/10.1016/j.annonc.2019.10.021.
75. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet*. 2020;396: 1090–1100. https://doi.org/10.1016/s0140-6736(20)31953-x.
76. Satoh T, Kang YK, Chao Y, et al. Exploratory subgroup analysis of patients with prior trastuzumab use in the ATTRACTION-2 trial: a randomized phase III clinical trial investigating the efficacy and safety of nivolumab in patients with advanced gastric/gastroesophageal junction cancer. *Gastric Cancer*. 2020;23:143–153. https://doi.org/10.1007/s10120-019-00970-8.
77. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382:810–821. https://doi.org/10.1056/NEJMoa1910549.
78. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *N Engl J Med*. 2021;384:1191–1203. https://doi.org/10.1056/NEJMoa2032125.
79. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22:512–524. https://doi.org/10.1016/s1470-2045(21)00005-x.
80. Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol*. 2021;22:450–462. https://doi.org/10.1016/s1470-2045(20)30737-3.
81. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198–211. https://doi.org/10.1016/s1470-2045(20)30641-0.
82. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. *Ann Oncol*. 2021;32:631–641. https://doi.org/10.1016/j.annonc.2021.01.071.
83. Winer EP, Lipatov O, Im SA, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:499–511. https://doi.org/10.1016/s1470-2045(20)30754-3.
84. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21:44–59. https://doi.org/10.1016/s1470-2045(19)30689-8.
85. Cohen JV, Dougan M, Zubiri L, et al. Liver biopsy findings in patients on immune checkpoint inhibitors. *Mod Pathol*. 2021;34:426–437. https://doi.org/10.1038/s41379-020-00653-1.
86. Tsung I, Dolan R, Lao CD, et al. Liver injury is most commonly due to hepatic metastases rather than drug hepatotoxicity during pembrolizumab immunotherapy. *Aliment Pharmacol Ther*. 2019;50:800–808. https://doi.org/10.1111/apt.15413.
87. da Silva JA, Falcão D, Cardoso C, et al. Hepatic immune-mediatedadverseeffects of immune checkpoint inhibitors: analysis of real-life experience. *Ann Hepatol*. 2021;26, 100561. https://doi.org/10.1016/j.aohep.2021.100561.
88. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med*. 2021;27:152–164. https://doi.org/10.1038/s41591-020-1131-x.
89. van Gerven NM, de Boer YS, Mulder CJ, et al. Auto immune hepatitis. *World J Gastroenterol*. 2016;22:4651–4661. https://doi.org/10.3748/wjg.v22.i19.4651.
90. 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;31:965–973. https://doi.org/10.1038/s41379-018-0013-y.
91. Regev A, Avigan MI, Kiazand A, et al. Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. *J Autoimmun*. 2020;114, 102514. https://doi.org/10.1016/j.jaut.2020.102514.
92. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) immunotherapy. *Cold Spring Harbor Perspect Biol*. 2018;10:a028456. https://doi.org/10.1101/cshperspect.a028456.
93. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract*. 2019;25: 551–557. https://doi.org/10.1177/1078155217745144.
94. Serviddio G, Villani R, Stallone G, et al. Tocilizumab and liver injury in patients with COVID-19. *Ther Adv Gastroenterol*. 2020;13, 1756284820959183. https://doi.org/10.1177/1756284820959183.
95. Zhang HC, Luo W, Wang Y. Acute liver injury in the context of immune checkpoint inhibitor-related colitis treated with infliximab. *J Immunother Cancer*. 2019;7:47. https://doi.org/10.1186/s40425-019-0532-1.
96. Shivaji UN, Jeffery L, Gui X, et al. Immune checkpoint inhibitor-associated gastrointestinal and hepatic adverse events and their management. *Ther Adv Gastroenterol*. 2019;12, 1756284819884196. https://doi.org/10.1177/1756284819884196.
97. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine*. 2018;61: 7–16. https://doi.org/10.1007/s12020-018-1588-2.