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Corticosteroids for high-grade immune checkpoint inhibitor-mediated hepatitis: is less more?

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ABBREVIATIONS

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IMH, immune checkpoint inhibitor-mediated hepatitis; irAEs, immune-related adverse events; mg/kg/d, milligram per kilogram per day; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

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Immune checkpoint inhibitors (ICIs) have transformed the field of oncology and improved outcomes in patients with difficult-to-treat malignancies. ICIs are monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CLTA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) that restore T-cell immune surveillance of tumors, but also relax the regulation of self-immunity, which can result in the development of immune-mediated organ toxicities. Consequently, ICI-mediated hepatitis (IMH) can occur in up to 16% of patients and usually presents with a hepatocellular pattern of injury. It is thought to be more common in those who receive CTLA-4 monotherapy or combination regimens of anti-CTLA-4 and either PD-1 or PD-L1 inhibitors.[1] The Common Terminology Criteria for Adverse Events (CTCAE) categorizes grade 3 or 4 toxicity as high-grade IMH and defines them as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation >5-20 times the upper limit of normal (ULN) and >20 times ULN, respectively.[1] Alkaline phosphatase and total bilirubin elevations can also be observed, but they are infrequent.[2] Multiple societies recommend high-dose corticosteroids, 1-2 milligram per kilogram per day (mg/kg/d) of methylprednisolone equivalents, for the management of high-grade IMH.[2] Currently, these recommendations rely on expert opinion

and small case series. Clinicians prefer to limit the use of high-dose steroids due to potentially higher rates of infection, hyperglycemia, low bone density, and uncertain effects on malignancy outcomes.[3-4]

A retrospective cohort study by Li *et al*. provides much-needed data to inform management of grade 3-4 IMH, including corticosteroid dosing, benefits of dose escalation, and frequency of adverse outcomes.[5] They analyze a large patient cohort who developed grade 3-4 IMH after receiving one or more ICIs between 2010 and 2020. 128 patients were initially treated with <1.5 mg/kg/d of methylprednisolone equivalents (the lower-dose group), while 87 patients were started on ≥1.5 mg/kg/d (the higher-dose group).

Does a higher starting dose or dose escalation result in more effective treatment of IMH? Li *et al.* reported no difference between the higher and lower-dose groups in time to ALT normalization as a primary study outcome (median 29 vs 28 days, *P*=0.83) and time to ALT improvement to ≤100 U/L as a secondary outcome (median 15 vs 14 days, *P*=0.72), even after Cox regression multivariate analysis adjusted for IMH severity and prior immune-related adverse events (irAEs) that were present in 46% of study patients. 20% of patients in the <1.5 mg/kg/d group were escalated to ≥1.5 mg/kg/d due to lack of response, but dose escalation was not associated with ALT normalization or faster ALT improvement. Despite intuitive expectations, the rate of steroid-refractory hepatitis (defined by the addition of a second immunosuppressant agent due to insufficient liver enzyme improvement) was similar in the two dose groups after adjusting for potential confounding variables including combination therapy, prior irAE, liver metastases presence, ALT at time of steroid initiation, age, sex, body mass index, diagnosis of melanoma, and pre-existing liver disease. However, compared to the lower-dose group, the higher-dose group patients more often received steroids intravenously, were exposed to >10 mg/day of prednisone longer, and were started on a second immunosuppressant faster.

Which adverse outcomes are worse with higher-dose steroids? In this study, higher-dose steroids were associated with more adverse outcomes, including infection (18% vs 7%, *P*=0.01) and hyperglycemia requiring treatment (23% vs 8%, *P*=0.001). The most common infections were pneumonia, Clostridioides difficile colitis, and urinary infection. There was no difference in the risk of gastrointestinal bleeding. Interestingly, the time to death in the melanoma patients in this study revealed no difference between the two steroid groups, even after correction for possible confounders.

How should underlying liver disease be approached? Patients with hepatocellular carcinoma (HCC) and autoimmune liver disorders were excluded from the Li *et al*. study. However, around a quarter of study patients had liver metastases and/or underlying liver disease, mostly non-alcoholic fatty liver; these patients were

equally present in the two steroid groups. ICIs are currently approved as a first line (combination of anti-PD-L1 atezolizumab and anti-VEGF bevacizumab) and second line (combination of anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab or anti-PD-1 pembrolizumab alone) therapy for advanced unresectable HCC in patients with compensated liver function bringing new considerations in IMH management.[4-6] In their clinical trials, high-grade hepatotoxicity ranged between 7% (single ICI agent) and 16% (ICI combination therapy), and resolved with high-dose corticosteroids, similar to other ICI indications. ICI appear to be safe in patients with viral hepatitis B and C, especially as antiviral therapy is usually continued to prevent HBV re-activation.[7] Diagnosis and management of high-grade IMH in HCC patients may be challenging and calls for more studies focused on patients with underlying, especially more advanced, liver disease. The effects of higher versus lower-dose steroids on viral hepatitis re-activation in the setting of IMH therapy are also still unknown.

What is next? The Li *et al*. study is one of the few studies providing evidence for clinical efficacy and lower rate of side effects on lower-dose steroids in IMH. Albeit, for most patients with high-grade IMH, the 1 mg/kg/d steroid dose will still be high (>60 mg/day). There are some additional limitations informing future studies. Over 90% of the Li *et al*. cohort were white, limiting applicability to patients of other races. Due to the retrospective nature of the study, it is unclear what factors influenced the decision to start a higher-dose steroids, but there are notable differences between the two groups. Potential risk factors for steroid therapy failure were more common in the higher-dose group, including grade 4 hepatotoxicity, prior irAE, and exposure to combination ipilimumab and nivolumab therapy, even if they were appropriately considered in the multivariate analysis and did not impact outcomes. Notably, some patients were already on corticosteroids for other irAEs or grade 1-2 IMH, but the time on steroids was counted starting on the day of the grade 3-4 IMH diagnosis; the distribution of this potential confounding variable is unclear between the two groups.
More data needs to be collected to determine the predictors of steroid-refractory IMH and its optimal management. In the Li *et al*. study, a second agent was added after one and two weeks of therapy with higher and lower-dose steroids, respectively, based on undefined criteria for response. It is unknown, if adding second-line agents (mycophenolate mofetil, tacrolimus, or azathioprine) earlier would shorten time to ALT normalization/improvement. Perhaps liver biopsy can assist in diagnosis and prognostication of steroid-refractory hepatitis. A randomized controlled trial is currently evaluating these second-line agents (NCT04810156).

Patients with organ transplants or autoimmune conditions who are on immunosuppression but develop malignancies treatable with ICIs are another special patient population. This patient category might potentially have higher rates of ICI complications, including organ rejection and autoimmune flare, as well as have longer

exposure and higher-dose steroids and higher degree of immunosuppression to treat hepatotoxicity. Finally, the CTCAE hepatotoxicity diagnosis relies on high levels of transaminases to define high-grade hepatitis, but this may not capture true clinical severity, which may be better reflected in other prognostic factors such as coagulopathy, hepatic encephalopathy, and presence of jaundice.[1]

In summary, Li *et al*. provide valuable support for initiation of steroids at lower doses without detriment to time to IMH improvement and with lower frequency of side effects (Fig. 1). Potentially randomized trials will be desirable to confirm the study findings and provide guidance for decision-making in management of IMH, which we will see more frequently as indications for ICIs are rapidly expanding.

REFERENCES

1. Peeraphatdit T, Wang J, Odenwald MA et al. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. Hepatology 2020;72(1):315-329.

2. De Martin E, Michot JM, Rosmorduc O et al. Liver Toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep 2020;2(6):100170.

3. Fardet L, Petersen I, Nazareth I. Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study. PLoS Med 2016;13:e1002024.

4. Chapman RW, Aspinall RJ, Trivedi P et al. Challenges in the use of corticosteroids in the management of autoimmune hepatitis. Br J Hosp Med 2019;80(10):594-599.

5. Li M, Wong D, Vogel AS et al. Effect of corticosteroid dosing on outcomes in high-grade immune checkpoint inhibitor hepatitis. Hepatology 2021; https://doi.org/10.1002/HEP.32215.

6. Finn RS, Qin S, Ikeda M et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. NEJM 2020;382:1894-1905.

7. Yau T, Kang YK, Kim TY et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA Oncol 2020;6(11):e204564.

8. Zhu AX, Finn RS, Edeline J et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-952.

9. Rico GT, Chan MM, Loo KF. The safety and efficacy of immune checkpoint inhibitors in patients with advanced cancers and pre-existing chronic viral infections (Hepatitis B/C, HIV): A review of the available evidence. Cancer Treat Rev 2020;86:102011.

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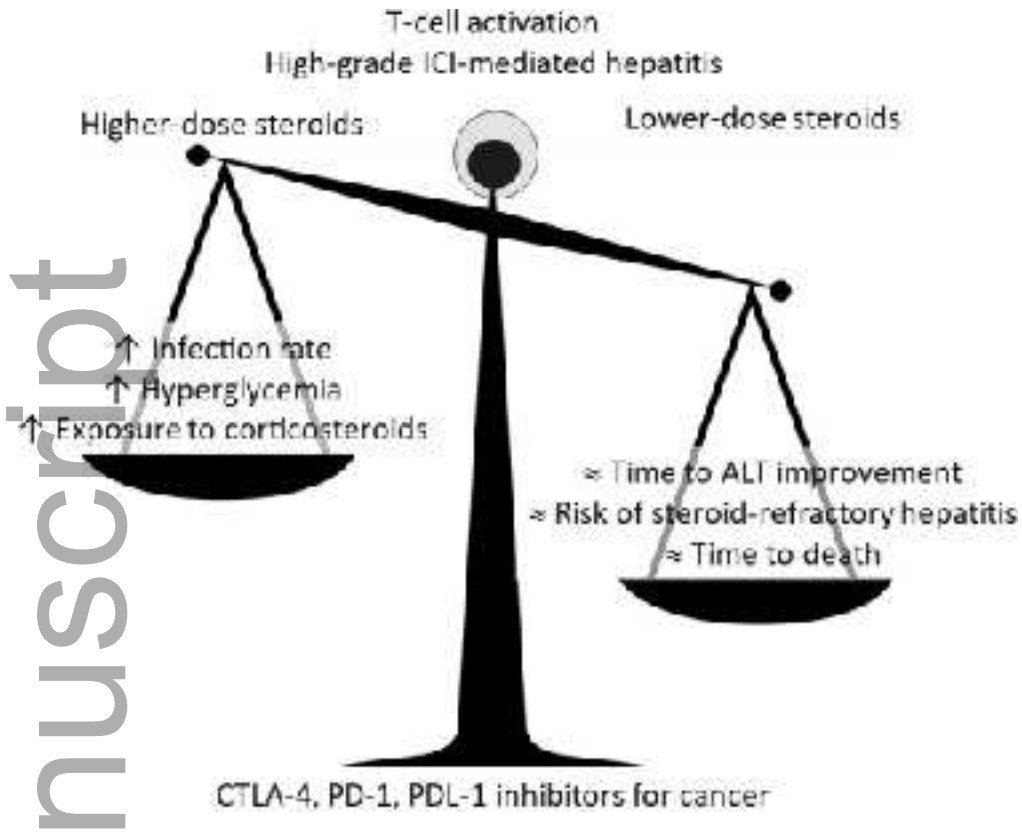
FIGURE LEGEND

Fig 1. Outcomes of steroid use in immune checkpoint inhibitor (ICI)-mediated hepatitis. Lower-dose steroids are associated with fewer side effects and similar outcomes in treatment of ICI-mediated hepatitis as compared to higher-dose steroids. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.



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