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EDITORIAL

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

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 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 because of 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 the management of grade 3–4 IMH, including corticosteroid dosing, benefits of dose escalation, and frequency of adverse outcomes.[5] They analyzed a large patient cohort who developed grade 3-4 IMH after receiving one or more ICIs between 2010 and 2020. One hundred twenty-eight patients were initially treated with <1.5 mg/kg/d of methylprednisolone equivalents (the lower-dose group), whereas 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 past immune-related adverse events (irAEs) that were present in 46% of study patients. Twenty percent of patients in the <1.5-mg/kg/d group were escalated to >1.5 mg/kg/d because of a 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 because of insufficient liver enzyme improvement) was similar in the two dose groups after adjusting for potential confounding variables, including combination therapy, past 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 i.v., were exposed to >10 mg/d 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 risk of gastrointestinal bleeding. Interestingly, time to death in

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IMH, ICI-mediated hepatitis; irAEs, immune-related adverse events; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

SEE ARTICLE ON PAGE 531

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 HCC and autoimmune liver disorders were excluded from the Li et al. study. However, around one quarter of study patients had liver metastases and/or underlying liver disease, mostly nonalcoholic 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.[6–8] 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. ICIs appear to be safe in patients with viral hepatitis B and C, especially given that antiviral therapy is usually continued to prevent HBV reactivation.[9] 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 reactivation 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/d). 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. Because of the retrospective nature of the study, it is unclear what factors influenced the decision to start 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, previous irAEs, 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.

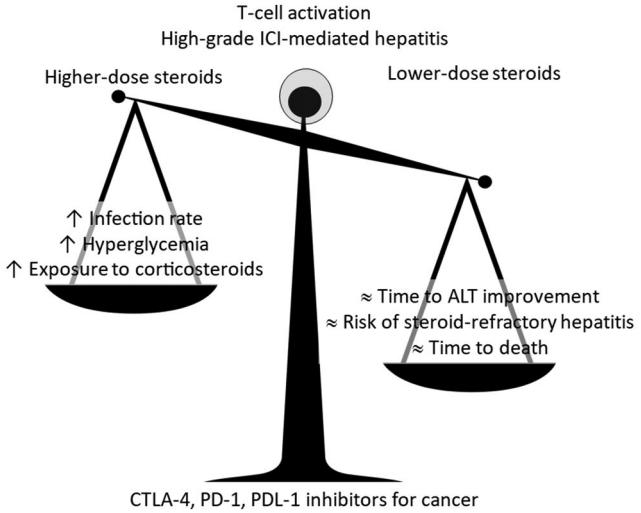

FIGURE 1 Outcomes of steroid use in ICI-mediated hepatitis. Lower-dose steroids are associated with fewer side effects and similar outcomes in treatment of ICI-mediated hepatitis as compared to higher-dose steroids

More data need 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 1 and 2 weeks of therapy with higher- and lower-dose steroids, respectively, based on undefined criteria for response. It is unknown whether adding second-line agents (mycophenolate mofetil, tacrolimus, or azathioprine) earlier would shorten time to ALT normalization/improvement. Perhaps liver biopsy can assist in the 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 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, HE, 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 a lower frequency of side effects (Figure 1). Potentially, randomized trials will be desirable to confirm the study findings and provide guidance for decision making in the management of IMH, which we will see more frequently given that indications for ICIs are rapidly expanding.

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CONFLICT OF INTEREST

Nothing to report.

AUTHOR CONTRIBUTIONS

NR and JJP developed the editorial outline; JJP drafted the article; NR and JJP developed a concept of the figure and contributed to the figure draft; NR revised the article critically for important intellectual content and approved the final version to be published.

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REFERENCES

1. Peeraphatdit T, Wang J, Odenwald MA, Hu S, Hart J, Charlton MR, et al. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. Hepatology. 2020;72:315–29.
2. De Martin E, Michot JM, Rosmorduc O, Guettier C, Samuel D. Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep. 2020;2:100170.
3. Fardet L, Petersen I, Nazareth I. Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study. PLoS Medicine. 2016;13:e1002024.
4. Chapman RW, Aspinall RJ, Trivedi P, Wright G, Heneghan M. Challenges in the use of corticosteroids in the management of autoimmune hepatitis. Br J Hosp Med. 2019;80:594–9.
5. Li M, Wong D, Vogel AS, Sack JS, Rahma OE, Hodi FS, et al. Effect of corticosteroid dosing on outcomes in high-grade immune checkpoint inhibitor hepatitis. Hepatology. 2022;75:531–40.
6. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382:1894–905.
7. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, 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:e204564.
8. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, 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;19:940–52.
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.