COMMENT
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Immune Checkpoint Inhibitors in Chronic Hepatitis B: Accelerating a Predetermined Outcome or Altering the Trajectory of Cure?

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Abstract: Immune checkpoint inhibitors (ICIs) are assessed for functional cure in chronic hepatitis B (CHB) patients with low baseline HBsAg, particularly those with cancer. While ICIs may accelerate serum hepatitis B surface antigen (HBsAg) clearance, overall rates show no significant advantage over other treatments. This questions whether ICIs fundamentally alter cure trajectories or merely hasten predetermined outcomes, rather than fundamentally altering the cure trajectory for a broader population. Given ICI side effects, costs, and the lack of predictive biomarkers, their clinical benefit for solely accelerating clearance is uncertain. Future research should clarify ICI mechanisms and identify robust biomarkers beyond HBsAg levels to guide patient selection and optimize therapy, emphasizing shared decision-making, especially for low HBsAg patients.

Keywords: Chronic hepatitis B; Immune checkpoint inhibitors; Functional cure; Predictive biomarkers.

Introduction

Achieving functional cure in chronic hepatitis B (CHB) remains a central yet elusive objective, as current nucleos(t)ide analogues (NAs) are mainly suppressive, and interferon (IFN)-based immunotherapies demonstrate limited efficacy and tolerability. Consequently, the quest for novel therapeutic strategies is ongoing.

We read with great interest the article by Mon et al. in the *Journal of Hepatology* reporting on the potential of functional cure for chronic hepatitis B by immune checkpoint inhibitor (ICI) therapy in cancer patients co-infected with HBV[1]. The study suggested that ICIs, particularly in patients with baseline serum hepatitis B surface antigen (HBsAg) level < 100 IU/mL, may accelerate HBsAg clearance[1]. The finding has sparked considerable discussion. Subsequent correspondence and the authors' reply have further underscored the complexity of this issue[2–4]. In this commentary, we summarize the findings of Mon et al., contextualize them within the broader landscape of CHB cure strategies, and argue for a more nuanced understanding of whether ICIs are acting as an "accelerant" or a "path-changer."

Summary of methods and results from Mon et al

This retrospective study recruited HBsAg-positive patients: consecutive patients with various cancers: pan-cancer patients receiving ICIs from May 2016 to Aug. 2020 (cohort 1, n = 118); hepatocellular carcinoma (HCC) patients receiving ICIs from Sep. 2020 to Oct. 2022 (cohort 2, n = 44, as validation); and an HBV-HCC control group receiving tyrosine kinase inhibitors (TKIs), selected from patients treated between Jan. 2014 and Jan. 2022 (cohort 3, n = 85), Factors for HBsAg loss or >1 log decline were analyzed.

Data from Mon et al. indicate that among HCC patients with baseline HBsAg < 100 IU/mL, the ICI-treated group (cohort 2) exhibited a significant time advantage in serological HBsAg clearance compared to the TKI-treated group (cohort 3), with median time to clearance of 11.4 months for cohort 2 and 55.1 months for cohort 3 (P = 0.0267), as revealed by Kaplan-Meier curve analysis[1].

As demonstrated in Figure 3A of Mon et al.'s paper, the endpoint HBsAg seroclearance rates in the HBsAg < 100 IU/mL subgroup were 5/32 (15.6%) in cohort 1 (ICI, pan-cancer patients), 4/18 (22.2%) in cohort 2 (ICI, HCC patients), and 3/20 (15.0%) in cohort 3 (TKI control, HCC patients), respectively[1]. Regrettably, comparison analysis revealed statistically significant differences neither between cohort 2 and cohort 3 (P = 0.687), nor between cohort 1 and cohort 3 (P = 1.000), as presented in Table 1. Indeed, Mon et al. also noted in their discussion that although ICIs demonstrated a higher monthly rate of HBsAg clearance in HCC patients with HBsAg < 100 IU/mL (reflecting a time advantage), the overall HBsAg clearance rates were not significantly different among the three groups[1].

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Table 1. Functional cure of chronic hepatitis B with immune checkpoint blockade immunotherapy based on PD-1/PD-L1 inhibitors in HBV-HCC patients[1].

Study Cohorts		Cohort 1 (n = 118)		Cohort 2 (n = 44)		Cohort 3 (n = 85)	
		Pan-Cancer patients receiving ICIs		HCC patients receiving ICIs		HCC patients receiving TKIs	
Baseline HBsAg level		< 100 IU/mL (31.1%)	≥ 100 IU/mL (68.9%)	< 100 IU/mL (51.4%)	≥ 100 IU/mL (48.6%)	< 100 IU/mL (27.8%)	≥ 100 IU/mL (72.2%)
Cumulative incidence of HBsAg loss (%)	Total	15.6% (5/32)	4.2% (3/71)	22.2% (4/18)	0% (0/17)	15% (3/20)	1.9% (1/52)
	12 months	11.0%	0%	13.0%	0%		
	24 months	16.3%	0%	38.4%	0%		

HBV, Hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

Discussion

The Central Dilemma: Acceleration vs. De Novo Induction

Coupled with the finding that the cumulative HBsAg disappearance rates with ICI strategies are comparable to the TKI group, a critical question may be raised: For these patients with baseline characteristics favorable for HBsAg seroclearance, does PD-1/PD-L1 inhibitor therapy primarily accelerate an HBsAg clearance process that was already destined to occur, rather than fundamentally altering the trajectory towards cure? Or, in other words, the role of ICIs might be more accelerative than *de novo* induction of clearance, if the anti-HBV specific immune function in such patients has already been partially recovered.

HBsAg disappearance rates with ICI strategies, as reported[1,4,5], are comparable to NA withdrawal strategy in populations with similar low HBsAg level (< 100 IU/mL)[6]. Furthermore, considering ICI-associated adverse events, costs[7], and lack of definitive predictive biomarkers, their application for CHB functional cure warrants cautious assessment if clinical benefit is mainly confined to accelerating clearance without improving overall rates versus lower-risk strategies like NA withdrawal, or add-on/switch to Pegylated -IFN based therapy[8]. In addition, the clinical benefit of accelerating HBsAg clearance in patients with low baseline levels is uncertain, particularly concerning the required duration to impact clinical outcomes and whether reduced viral exposure lessens hepatocellular carcinoma risk. Investigating these points is essential to establish the clinical relevance of such "acceleration".

The clinical value of this acceleration is debatable. While earlier clearance is intuitively positive, the tangible long-term benefit for an individual patient—particularly in reducing the lifelong risk of HCC—is not yet proven. If the outcome was predetermined, a strategy with lower risk, such as monitored NA cessation, might be equally effective over a slightly longer timeframe.

Safety remains a paramount concern in ICI therapy. A large-scale meta-analysis indicated an overall immune-related adverse events (irAEs), incidence of 17.1% (1111/6507), with 4% (196/4921) classified as grade 3[9], and 0.4–1.2% resulting in fatality[7]. Beyond encompassing multiple organ systems—including rheumatic, digestive, cardiovascular, respiratory, and neurological tissues—ICIs can notably disrupt the endocrine system and gonadal axis[10]. Crucially, emerging evidence highlights the neglected burden of chronic irAEs: approximately 60.4% of patients manifest persistent symptoms even after treatment discontinuation[11]. Notebly, it is imperative to extend the surveillance window, shifting focus from solely acute management to comprehensive longitudinal monitoring of these adverse events.

Immunological Underpinnings

The "acceleration" phenomenon may be rooted in the unique state of T-cell dysfunction in CHB. Although a baseline HBsAg < 100 IU/mL is a favorable prognostic marker[1,12,13], it may indicate a shared underlying immunological prerequisite—namely, that a lower viral antigen burden could reflect a state of reduced immunosuppression or less profound T-cell exhaustion. The HBV-specific $CD8^+$ T-cell response is often characterized by an atypical dysfunction (tolerance/anergy, not classical exhaustion) where current ICIs alone may be suboptimal compared to co-stimulatory strategies[14,15]. This suboptimal T-cell response to ICIs suggests a constrained therapeutic effect, potentially a spectrum from accelerated clearance to possessing a certain potential to alter the therapeutic trajectory only if epigenetic regulation is not fixed[16]. This suggests a "therapeutic ceiling" for monotherapy with current ICIs.

Clinical Implications and Shared Decision-Making

These insights have direct clinical consequences. For patients with very low HBsAg, a therapeutic decision point arises: "gentle induction" (e.g., NA cessation[12,13]) or "active reinforcement" (e.g., ICIs). The decision must weigh the potential for faster clearance against the risks of immune-related adverse events (irAEs), financial toxicity, and the uncertainty of long-term benefit. If ICIs primarily accelerate a predetermined outcome in these patients, then for selected low HBsAg individuals (e.g., elderly with minimal liver disease) with reasonable spontaneous clearance probability[17,18], a "watchful waiting" strategy of monitored NA cessation might be more appropriate.

This complexity underscores the paramount importance of shared decision-making (SDM) and Crucially SDM respected patient preferences and quality of life amidst uncertainties warrants greater emphasis in guidelines for this subgroup. For an elderly patient with minimal liver fibrosis, the risks of ICI therapy may outweigh the benefits of accelerated clearance. For a younger patient or one with a family history of HCC, the same acceleration might be deemed highly valuable. Future clinical guidelines for this subgroup must move beyond a one-size-fits-all approach and explicitly incorporate SDM frameworks.

The Path Forward: Mechanisms and Biomarkers

To move the field forward, future research must transition from asking if ICIs work to how, for whom, and when. Detailed profiling of HBV-specific T-cell function, transcriptomics, and epigenetics before, during, and after ICI therapy to define the molecular signature of response. Developing predictive biomarkers that go

beyond HBsAg level. These could include: (1) T-cell Repertoire and Phenotype: The presence of a stem-like memory T-cell population capable of expansion upon PD-1 blockade. (2) Serological Profiles: Levels of cytokines like IL-21 or soluble immune checkpoints. (3) Liver Microenvironment: Non-invasive markers of intrahepatic immune activity. The goal is to identify the patient in whom ICIs will "unlock" a durable, enhanced immune control (altering the trajectory) versus the one in whom it will simply "press fast-forward" on a predetermined outcome.

Conclusion

The study by Mon et al. provides a crucial piece of the puzzle, demonstrating that ICIs can accelerate HBsAg clearance in a favorable subgroup of CHB patients. However, the lack of a significant improvement in overall cure rates suggests their primary role may be that of an accelerant rather than a universal path-changer. To realize the full potential of immunotherapies in CHB, future research must elucidate ICI immunological mechanisms in CHB to define their role and appropriate patient populations for functional cure, particularly considering the ethical implications related to risk-benefit, overtreatment, and optimal intervention timing. This necessitates robust biomarkers beyond HBsAg levels—reflecting T-cell status or liver immune milieu—to differentiate patients with only accelerated clearance from those for whom ICIs could provide an enhanced, durable cure.

Abbreviations

CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICIs, Immune checkpoint inhibitors; IFN, interferon; irAEs, immune-related adverse events; NAs, nucleos(t)ide analogues; SDM, shared decision-making; TKI, tyrosine kinase inhibitor.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Authors' contributions

LLW: conceptualization and writing-original draft; BJ: methodology and writing-original draft; FML: critical review and study supervision.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Chat GPT(OpenAI) to refine English language expression and improve textual clarity. The output was subsequently reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the final content.

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