

Chronic hepatitis B: Is PD-1 blockade the key to T-cell revival?

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Chronic hepatitis B (CHB) remains a significant global health challenge, with current antiviral therapies effectively suppressing viral replication but rarely achieving a functional cure, defined by sustained hepatitis B surface antigen (HBsAg) loss. The persistent presence of HBsAg indicates ongoing viral activity and a heightened risk of liver complications. This unmet need drives the search for novel approaches that can induce HBsAg reduction and restore immune control.

A recent study published in *Gut* investigated whether a 24-week anti-PD-1 antibody regimen could promote HBsAg reduction and concurrently enhance HBV-specific T cell responses in patients with CHB. The findings suggest that targeting the PD-1 pathway may offer a viable strategy for achieving functional cure in this challenging patient population.¹

KEY TAKEAWAYS

- The Pivot: A 24-week anti-PD-1 regimen achieved HBsAg reduction and improved HBV-specific T cell responses in CHB patients.
- The Data: HBsAg reduction occurred in 40% of patients (4/10) after 24 weeks of treatment.
- The Action: Clinicians should monitor the evolving landscape of immune checkpoint inhibitors for CHB, particularly as longer-term data and larger trials emerge.

Chronic hepatitis B is a complex disease characterized by persistent viral infection and impaired host immune responses. The programmed cell death protein 1 (PD-1) pathway plays a critical role in T cell exhaustion, a phenomenon where T cells lose their effector functions during chronic infections, including HBV. Blocking this pathway with anti-PD-1 antibodies aims to reinvigorate these exhausted T cells, allowing them to clear infected hepatocytes and reduce viral load. This approach has seen success in oncology, and its application in chronic viral infections represents a logical extension of its immunomodulatory effects.¹

He, Chen, and Liu conducted a study involving 10 patients with chronic hepatitis B who received a 24-week regimen of an anti-PD-1 antibody. The investigators focused on patients with detectable HBsAg and HBV DNA, aiming to assess both serological and immunological endpoints. They measured HBsAg levels, HBV DNA, and characterized HBV-specific T cell responses before and after treatment. The trial design was open-label, without a placebo comparator, which is a common starting point for novel immunotherapies in difficult-to-treat conditions.¹

The Immunological Reinvigoration

The primary objective of the study was to evaluate the impact of anti-PD-1 therapy on HBsAg levels and HBV-specific T cell responses. After 24 weeks of treatment, 40% of patients (4/10) achieved HBsAg reduction, defined as a decrease from baseline. This reduction was accompanied by a concurrent enhancement of HBV-specific T cell responses, indicating that the PD-1 blockade successfully reinvigorated the immune system. The T cell responses were measured by interferon-gamma (IFN- γ) production upon stimulation with HBV antigens, a key marker of effective antiviral immunity.¹

Specifically, the researchers observed an increase in the frequency and functionality of HBV-specific CD8⁺ T cells in responders. These cells are essential for clearing virally infected cells. The improved T cell function correlated with the observed HBsAg reduction, suggesting a direct link between immune restoration and viral control. This finding aligns with the theoretical basis for PD-1 blockade in chronic infections, where reversing T cell exhaustion is paramount. The study did not, however, provide data on sustained HBsAg seroconversion or functional cure rates beyond the 24-week treatment period, which remains a critical long-term goal for CHB management.¹

But, the study also reported a decrease in HBV DNA levels in some patients, though this was not the primary endpoint. The median reduction in HBV DNA was modest, but the immunological changes were more pronounced. This suggests that while direct viral suppression may not be the immediate effect, the immune system is being primed for a more effective long-term response. The study did not include a comparator arm, so the observed effects cannot be definitively attributed solely to the anti-PD-1 antibody without confounding factors. This is a common limitation in early-phase trials of novel agents.¹

The safety profile of the anti-PD-1 regimen was generally consistent with what is known for this class of drugs in oncology, with no new or unexpected safety signals reported in this small cohort. Adverse events were manageable and did not lead to treatment discontinuation in any patient. This is an important consideration for a chronic condition like hepatitis B, where long-term tolerability is essential. The small sample size, however, limits the generalizability of these safety findings, and larger trials will be necessary to fully characterize the safety profile in CHB patients. For a broader understanding of liver diseases, including chronic hepatitis, clinicians may find *Sherlock's Diseases of the Liver and Biliary System* a valuable reference.¹

What the trial actually measured

The trial focused on HBsAg reduction and HBV-specific T cell responses as key indicators of treatment efficacy. HBsAg reduction is a surrogate marker for functional cure, which is the ultimate goal in CHB therapy. While complete HBsAg seroconversion (loss of HBsAg and appearance of anti-HBs antibodies) is the gold standard, any significant reduction in HBsAg levels is considered a positive step, as it correlates with improved long-term outcomes and reduced risk of hepatocellular carcinoma. The study's emphasis on immunological endpoints provides mechanistic insight into how PD-1 blockade might achieve these serological changes.¹

The measurement of HBV-specific T cell responses involved sophisticated immunological assays, including flow cytometry and ELISpot, to quantify IFN- γ production. These methods provide a direct assessment of T cell functionality and their ability to recognize and respond to HBV antigens. The increase in these responses after treatment directly supports the hypothesis that PD-1 blockade reverses T cell exhaustion. This is a critical distinction from traditional antiviral therapies, which primarily target viral replication but do not directly restore host immunity. The study did not, however, explore the durability of these enhanced T cell responses beyond the 24-week treatment period, which is

essential for sustained viral control.¹

But, the trial's duration of 24 weeks is relatively short for a disease like CHB, which often requires lifelong management. While the initial HBsAg reduction and immune enhancement are encouraging, the long-term impact on disease progression, liver fibrosis, and hepatocellular carcinoma incidence remains unknown. Future studies will need to follow patients for extended periods to determine if these early benefits translate into sustained clinical improvements. The patient population was also relatively small, consisting of only 10 individuals, which means the results should be interpreted with caution. Larger, multicenter trials with diverse patient populations are necessary to confirm these preliminary findings and establish the optimal duration and dosing of anti-PD-1 therapy.¹

The open-label design is the obvious caveat. Without a control group receiving placebo or standard of care, it is challenging to definitively attribute all observed changes solely to the anti-PD-1 antibody. While the immunological changes are compelling, the lack of a comparator means that some HBsAg fluctuations could potentially be part of the natural history of the disease or influenced by other unmeasured factors. This is a common limitation in early-phase studies, but it highlights the need for randomized controlled trials to validate these results. For clinicians managing complex chronic conditions, understanding the nuances of trial design is as important as the results themselves, as explored in our coverage on Bryan Johnson's Chronic Disease: A Diagnostic Labyrinth.¹

The Road Ahead for Immune Checkpoint Inhibitors in CHB

The findings from He, Chen, and Liu provide a compelling rationale for further investigation into anti-PD-1 antibodies as a therapeutic strategy for chronic hepatitis B. The ability to reduce HBsAg and enhance HBV-specific T cell responses within a relatively short treatment window suggests a shift from purely antiviral suppression to immune-mediated viral control. This approach could offer a pathway to functional cure for patients who currently have limited options beyond lifelong nucleos(t)ide analogue therapy. The mechanism of action, by reversing T cell exhaustion, directly addresses a core immunological defect in CHB.¹

Still, several questions remain unanswered. The optimal patient population for anti-PD-1 therapy in CHB needs to be precisely defined. Factors such as baseline HBsAg levels, HBV DNA, HBeAg status, and the degree of liver inflammation may influence treatment response. Identifying biomarkers that predict response would be important for patient selection and maximizing the benefit-risk ratio. The study did not examine these subgroup analyses due to its small sample size, but future research must address these critical aspects. The potential for combination therapies, perhaps with existing antivirals or other immunomodulatory agents, also warrants exploration.¹

The long-term safety and efficacy of anti-PD-1 antibodies in CHB patients are also paramount. While the 24-week safety profile was acceptable, chronic administration of immune checkpoint inhibitors can lead to immune-related adverse events (irAEs) affecting various organ systems. The balance between achieving viral control and managing potential irAEs will be a key consideration for clinical practice. The durability of HBsAg reduction and HBV-specific T cell responses after treatment cessation will also determine the true clinical utility of this approach. This is particularly relevant given the chronic nature of HBV infection and the need for sustained remission.¹

The next steps will undoubtedly involve larger, randomized, placebo-controlled trials to confirm these preliminary findings and establish the definitive role of anti-PD-1 antibodies in CHB management. These trials should also investigate different dosing regimens, treatment durations, and combination strategies to optimize outcomes. The ultimate goal is to achieve a functional cure, and while this study represents a significant step forward, the journey is far from over. The

data from this trial will inform the design of these larger studies, moving the field closer to a potential new therapeutic option for millions of patients worldwide. For those interested in the broader context of infectious disease management, the Oxford Handbook of Infectious Diseases and Microbiology offers a comprehensive guide.¹

CLINICAL IMPLICATIONS

The prospect of HBsAg reduction through immune checkpoint blockade in chronic hepatitis B is genuinely intriguing for clinicians. Current therapies, while effective at suppressing viral load, rarely offer a functional cure, leaving patients with ongoing risks. This study, albeit small, provides a mechanistic rationale for targeting PD-1 to reinvigorate exhausted T cells, a critical step towards immune control.

But, the 24-week duration and open-label design mean we must temper enthusiasm with pragmatism. A 40% HBsAg reduction in a cohort of 10 patients is a signal, not a definitive answer. We need larger, randomized trials with longer follow-up to understand if these early immunological shifts translate into sustained HBsAg loss and improved clinical outcomes, particularly in diverse patient populations.

The safety profile, consistent with oncology experience, is reassuring for a chronic condition. But, the long-term implications of immune-related adverse events in a non-oncology setting, where patients may be treated for extended periods, require careful monitoring. This is not a drug to prescribe lightly without robust phase 3 data and clear guidelines on patient selection and adverse event management.

For now, this research provides a strong foundation for future studies, pushing the field beyond mere viral suppression. Clinicians should watch for subsequent trials that will hopefully clarify the role of anti-PD-1 antibodies, alone or in combination, in achieving a functional cure for chronic hepatitis B.

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REFERENCES

1. He T, Chen M, Liu M. Twenty-four-week anti-PD-1 antibody regimen promoted HBsAg reduction and concurrently enhanced HBV-specific T cell responses in patients with chronic hepatitis B. Gut 2026. PMID: 41443982.

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