Immune Checkpoint Inhibitors (ICI) in the Functional Cure of Hepatitis B: A Narrative Review

I Komang Wisuda Dwija Putra[*], *I Ketut Mariadi*[**], *Gde Somayana*[**]

*Bali Mandara General Hospital, Bali, Indonesia

**Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Udayana University/ Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Indonesia

Corresponding author:
I Komang Wisuda Dwija Putra, Bali Mandara General Hospital, Bali, Indonesia, Email: wisudadwija@gmail.com

ABSTRACT

Chronic hepatitis B (CHB) remains a major global health burden, largely due to the persistence of covalently closed circular DNA (cccDNA) within infected hepatocytes, which hinders complete viral eradication despite long-term antiviral therapy. In recent years, immune checkpoint inhibitors (ICIs) have emerged as a potential therapeutic strategy by restoring exhausted antiviral immune responses. This review explores the mechanisms of action of ICIs, their current application in hepatitis B virus (HBV) infection, and their potential role in achieving a functional cure. Available evidence indicates that ICIs targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) are capable of partially restoring HBV-specific T-cell function and reducing intrahepatic cccDNA transcriptional activity. Early-phase clinical studies have demonstrated encouraging outcomes, including declines in hepatitis B surface antigen (HBsAg) levels and occasional HBsAg loss; however, consistent achievement of a functional cure remains limited. Notably, combination strategies involving ICIs with therapeutic vaccines or nucleos(t)ide analogues appear to enhance antiviral efficacy compared with monotherapy. In conclusion, ICIs represent a promising adjunctive approach for CHB treatment and may contribute to the pursuit of a functional cure. Nevertheless, further well-designed clinical trials are required to establish their long-term safety, optimal treatment combinations, and effectiveness, particularly in HBV-endemic populations.

***Keywords**: Functional Cure, Hepatitis B, Immune Checkpoint Inhibitor*

ABSTRAK

Hepatitis B kronis masih merupakan beban kesehatan global yang signifikan, terutama akibat persistensi covalently closed circular DNA (cccDNA) di dalam hepatosit yang terinfeksi, yang menyebabkan eradikasi virus secara total sulit dicapai, meskipun sudah diberikan antivirus jangka panjang. Dalam beberapa tahun terakhir, immune checkpoint inhibitors (ICIs) muncul sebagai terapi potensial melalui kemampuannya memulihkan respons antivirus yang mengalami kelelahan. Tinjauan ini bertujuan untuk mengeksplorasi mekanisme kerja ICIs, dalam pengobatan infeksi virus hepatitis B (HBV), serta potensi perannya dalam mencapai functional cure. Hasil penelusuran menunjukkan bahwa ICIs yang menargetkan programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), dan cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) berpotensi mengembalikan fungsi sel T spesifik HBV serta menurunkan aktivitas transkripsi cccDNA intrahepatik. Uji klinis fase awal menunjukkan hasil yang menjanjikan, seperti penurunan kadar atau hilangnya (HBsAg) maupun tercapainya functional cure secara konsisten masih terbatas. Strategi kombinasi ICIs dengan vaksin terapeutik atau analog nukleos(t)ida dilaporkan dapat meningkatkan efektivitas antivirus dibandingkan monoterapi.

Secara keseluruhan, ICIs merupakan terapi adjuvan yang menjanjikan dalam penanganan HBK dan berpotensi mencapai functional cure, namun masih diperlukan uji klinis lebih lanjut untuk menilai keamanan, efektivitas jangka panjang, serta aplikabilitasnya pada populasi dengan endemisitas HBV tinggi.

Kata kunci: *Penyembuhan Fungsional, Hepatitis B, Inhibitor Pos Pemeriksaan Kekebalan Tubuh*

INTRODUCTION

Hepatitis B remains a significant global health threat, being a potentially fatal liver infection caused by the hepatitis B virus (HBV). The virus primarily spreads through contact with body fluids such as blood, semen, and vaginal secretions.[1] Global estimates indicate that over two billion people have been infected with HBV, with 248 million individuals living with chronic infection. According to the Global Burden of Disease study, hepatitis B was responsible for 686,000 deaths in 2013, resulting in a global mortality rate of 5.9 per 100,000 population. Among these deaths, 300,000 were attributed to liver cancer and 317,400 to liver cirrhosis caused by hepatitis B.[2] The incidence of HBV-related deaths has shown a concerning increase, with a 5.9% rise between 1990 and 2019 and a 2.9% rise between 2015 and 2019.[3] The management of chronic hepatitis B (CHB) has traditionally relied on nucleotide analogues (NUCs) and interferon therapies. NUCs can suppress viral replication effectively during treatment; however, the recurrence of viral activity following cessation of therapy underscores the need for prolonged, potentially lifelong treatment.[4] While NUCs can suppress HBV replication, they fail to target the covalently closed circular DNA (cccDNA) within hepatocytes, the stable form of the viral genome that contributes to chronic infection. This necessitates ongoing treatment, which poses significant challenges, particularly in resource-limited settings with inconsistent healthcare access.[5]

The persistence of covalently closed circular DNA (cccDNA) in infected hepatocytes, coupled with immune system impairment caused by chronic HBV infection, significantly complicates efforts to cure chronic hepatitis B (CHB). Although antiviral agents can effectively suppress viral replication, they are inadequate in eliminating the virus due to the stable nature of cccDNA, which is resistant to existing therapies.[6] Additionally, resistance to nucleoside analogs, particularly those with a low barrier to resistance such as lamivudine, further complicates treatment and necessitates alternative regimens.[7] The heterogeneity of HBV genotypes adds another layer of complexity, influencing treatment responses and outcomes, and thus requiring personalized approaches to therapy.[8,9] The emergence of resistant viral strains can complicate therapy, necessitating alternative treatment regimens and careful management of antiviral therapy adjustments.[7,10] Additionally, the heterogeneity of viral genotypes can affect treatment responsiveness and the overall prognosis of HBV infection, necessitating a more personalized approach to therapy.[6,11]

Innovative therapeutic approaches, including immune checkpoint inhibitors (ICIs), are emerging as potential treatments for chronic hepatitis B (CHB) due to their ability to counteract immune suppression and reactivate antiviral T cell responses, which are essential for eliminating HBV.[12] Immune checkpoint inhibitors (ICIs) work by restoring the function of exhausted T cells, thereby enhancing the immune system's ability to fight HBV, including targeting liver cells harboring covalently closed circular DNA (cccDNA), a major barrier to viral clearance.[13,14] However, it remains uncertain whether ICIs contribute positively to HBV viral control or lead to HBsAg seroclearance, especially at the doses used for cancer treatment. HBV reactivation is also a concern in clinical trials, and there is a lack of studies evaluating the use of ICIs specifically for HBV infection. This review aims to explore the mechanisms of ICIs in treating hepatitis B, their potential for achieving a functional cure, and the future directions of this treatment approach.

Despite substantial advances in antiviral therapy, achieving a functional cure for chronic hepatitis B (CHB) remains a major unresolved clinical challenge. Current treatments with nucleos(t)ide analogues and interferon are effective in suppressing hepatitis B virus (HBV) replication but fail to eradicate or durably silence covalently closed circular DNA (cccDNA), necessitating long-term therapy and leaving underlying immune dysfunction uncorrected. Chronic HBV infection is characterized by profound exhaustion of HBV-specific T-cell responses, which limits spontaneous viral clearance and represents a key barrier to functional cure. In this context, immune checkpoint inhibitors (ICIs) have emerged as a promising immunotherapeutic strategy due to their ability to restore exhausted antiviral T-cell activity. However, existing evidence on the role of ICIs in HBV infection remains fragmented and

largely indirect, as most available data originate from oncology settings in which HBV-related outcomes are secondary observations rather than primary study endpoints. Consequently, critical gaps persist regarding the efficacy, safety, optimal therapeutic context, and mechanistic impact of ICIs on cccDNA transcriptional activity and hepatitis B surface antigen (HBsAg) seroclearance in non-oncologic CHB populations. Additional uncertainties include the influence of HBV genotype heterogeneity on immune responsiveness, as well as concerns related to viral reactivation and immune-mediated hepatotoxicity following immune checkpoint blockade. These limitations underscore the absence of a comprehensive and focused synthesis integrating immunological mechanisms, clinical evidence, and safety considerations of ICIs within the framework of functional cure for hepatitis B.

To ensure a comprehensive and structured synthesis of the available evidence, a literature search was conducted using electronic databases including PubMed/MEDLINE, Scopus, and Web of Science. The search strategy incorporated combinations of the following keywords and Medical Subject Headings (MeSH) terms: “hepatitis B”, “chronic hepatitis B”, “HBV”, “immune checkpoint inhibitor”, “PD-1”, “PD-L1”, “CTLA-4”, “nivolumab”, “pembrolizumab”, “envafolimab”, “therapeutic vaccine”, “functional cure”, “HBsAg seroclearance”, and “HBV reactivation”. The search was limited to studies published between 2015 and 2025, in accordance with the time frame represented in the cited literature, and to capture evidence from the modern immunotherapy era.

Eligible studies included clinical trials (phase 1–3), observational cohort studies, case series, translational immunology studies, and relevant narrative or systematic reviews addressing immune checkpoint inhibition in the context of HBV infection. Both oncologic studies reporting HBV-related outcomes and studies specifically conducted in chronic hepatitis B populations were considered. Only articles published in English were included. In addition, the reference lists of selected articles were manually screened to identify further relevant studies.

CHALLENGES OF TREATING HEPATITIS B

HBV replicates at an extremely high rate, with an estimated daily production of up to one trillion (10^{12}) virions. In addition to fully formed virions, HBV also generates subviral particles composed solely of surface proteins. These subviral particles cannot replicate or cause infection, but they are produced at levels over 1,000 times higher than complete virions. The large quantity of circulating HBsAg from these particles is believed to contribute to immune exhaustion in chronic HBV infection. One of the primary obstacles in curing HBV is the persistence of covalently closed circular DNA (cccDNA), which is located in the nuclear hepatocyte and the intracellular recycling of nucleocapsids. This cccDNA acts as a template for the transcription of all HBV RNAs, including pregenomic RNA (pgRNA), which is reverse transcribed into HBV DNA, as well as messenger RNAs that are translated into viral proteins. In vitro research indicates that interferon (IFN) can directly impact cccDNA by promoting its degradation and/or suppressing its transcription, which helps explain the higher rates of HBeAg and HBsAg clearance seen with IFN compared to nucleos(t)ide analogues (NUCs). In contrast, NUCs lack direct activity against cccDNA, resulting in only minimal reductions in cccDNA levels even after prolonged treatment.[15]

An additional challenge is that HBV DNA can integrate into the host genome. While integrated HBV DNA cannot replicate, it often retains the full-length S gene, which can continue to produce HBsAg—especially in HBeAg-negative individuals. Therefore, achieving a cure for HBV will require long-term inhibition of both cccDNA and transcription from integrated HBV DNA, as well as the restoration of HBV-specific immune responses to maintain immune control.[15]

IMMUNE CHECKPOINT INHIBITOR (ICIs)

Immune checkpoint inhibitors (ICIs) are a form of immunotherapy that enhances the immune system’s ability to combat cancer by targeting and blocking certain proteins that typically act as restraints on immune activity. These "checkpoint" proteins normally help regulate the immune response to prevent it from becoming overactive or attacking the body’s own tissues. Still, they can also enable cancer cells to escape immune detection.[16] Immune checkpoint inhibitors (ICIs) help alleviate the immunosuppression mediated by immune checkpoints, thereby partially restoring the antiviral activity of T cells against HBV. When used in combination with other therapies, ICIs have shown both safety and effectiveness in the treatment of patients with chronic hepatitis B (CHB).[14]

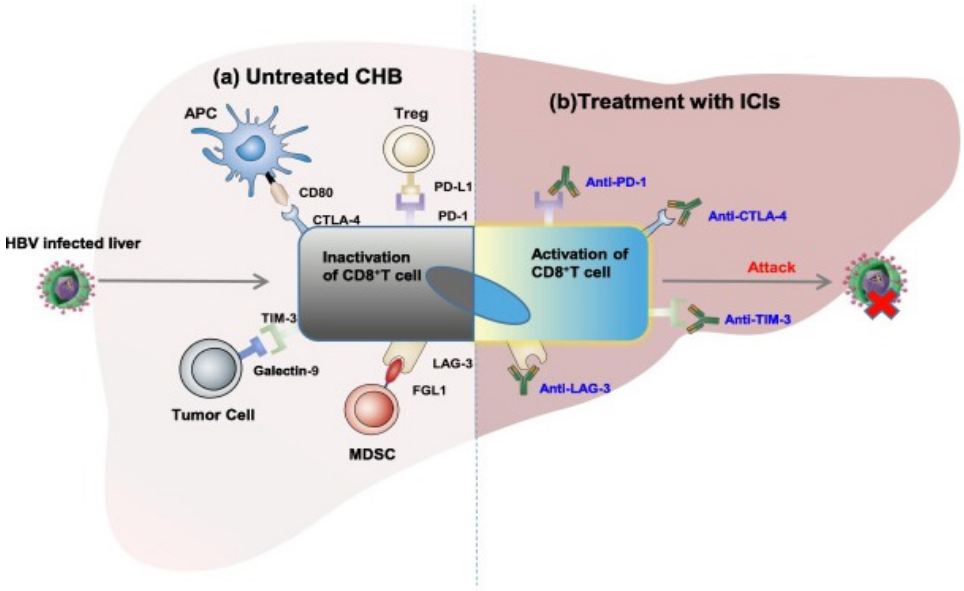

Figure 1. Immune checkpoint inhibitors (ICIs) hold potential as a treatment for chronic hepatitis B (CHB). (A) In untreated CHB, HBV-specific CD8+ T cells express elevated levels of multiple immune checkpoint molecules, leading to their functional exhaustion and reduced capacity to eliminate HBV. Specifically, PD-1 interacts with PD-L1, CTLA-4 with CD80, TIM-3 with Galectin-9, and LAG-3 with FGL1; each interaction suppresses the activity of HBV-specific CD8+ T cells, hindering viral clearance. (B) Administration of ICIs can block these checkpoint pathways, reactivating HBV-specific CD8+ T cells and enhancing their ability to clear the virus.[14]

Several immune checkpoint inhibitors (ICIs) have been developed **(Figure 1),** including antibodies that target PD-1 (such as nivolumab), PD-L1 (such as atezolizumab and durvalumab), and cytotoxic T-lymphocyte-associated protein 4 (such as tremelimumab).[17,18] Currently, the immune checkpoints that have been effectively targeted with approved immune checkpoint inhibitors (ICIs) include CTLA-4, PD-1 (CD279), its ligand PD-L1 (CD274), and LAG-3 (CD223). Other co-inhibitory immune checkpoints under investigation include T-cell immunoglobulin and mucin-domain-containing-3 (TIM-3, CD366), T-cell immunoglobulin and ITIM domain (TIGIT), V-domain Ig suppressor of T-cell activation (VISTA), among others.[16]

MECHANISM OF ACTION

Broad, durable, and strong antiviral T cell responses are recognized as crucial for achieving viral clearance and eliminating cccDNA in cases of spontaneous, self-limited HBV infection. Consequently, various approaches are being investigated to enhance the weakened HBV-specific T cell responses in individuals with chronic HBV. One of those strategies includes immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies.[19]

Immune checkpoint inhibitors (ICIs) work by blocking specific proteins (like PD-1, PD-L1, CTLA-4, TIM-3, etc) that normally prevent T cells from attacking cancer cells or other targets. This allows the immune system to recognize and destroy these cells, which is the foundation of their therapeutic effect in cancer and potentially other diseases like viral infections. In the context of Hepatitis B virus (HBV) and cccDNA, ICIs are being investigated as a potential treatment strategy to enhance immune responses against the virus and potentially reduce cccDNA levels.[14]

Checkpoint inhibitors like nivolumab and pembrolizumab, which target the programmed death-1 (PD-1) pathway specifically, have shown considerable promise in restoring T-cell activity in patients with hepatocellular carcinoma (HCC) linked to chronic hepatitis B virus (HBV) infection. These inhibitors function by preventing the interaction between PD-1 on T cells and its ligands, PD-L1 and PD-L2, which are frequently elevated in the tumor microenvironment and HBV-infected liver tissue. By doing so, they help revive T-cell activity, reduce T-cell exhaustion, and strengthen the immune system's response against the virus. In a key study, they demonstrated the potential of PD-1 inhibitors in HBV treatment, showing that they can enhance the immune system's ability to fight HBV by reversing T-cell dysfunction. Currently, there is no direct evidence demonstrating that immune checkpoint inhibitors (ICIs) can eliminate intrahepatocytic covalently closed circular DNA (cccDNA). However, ICIs may indirectly influence cccDNA transcriptional activity by restoring antiviral T-cell responses within the hepatic microenvironment. This strategy reflects a

growing focus on using immune checkpoint blockade as an innovative approach to manage HBV-related liver diseases, including liver cancer.[5,20,21]

PD-1 inhibitors

PD-1 inhibitors can help reverse T-cell dysfunction in the liver, enhance the performance of HBV-specific CD8+ and CD4+ T cells, and restore the secretion of IL-2 and IFN-γ by HBV-specific CD8+ T cells, thereby improving the clearance of HBV. Even when CD4+ helper T cells are suppressed, PD-1 blockade still supports the recovery of CD8+ T-cell function. While PD-1 inhibitors boost CD8+ T-cell activation, they may also suppress their proliferation. In this context, the CD28/B7 co-stimulation pathway is promising, as it plays a vital role in T-cell proliferation following PD-1 inhibition. Thus, to enhance HBV clearance through T-cell responses, therapeutic strategies should focus on both restoring the function of HBV-specific CD8+ T cells and promoting their proliferation. This might be achieved by combining PD-1 inhibitors with activation of the CD28 pathway in the treatment of chronic hepatitis B (CHB). CHB has a notable impact on humoral immunity, and PD-1 inhibitors are known to affect both cellular and humoral immune responses. These inhibitors have been shown to facilitate the maturation of HBsAg-specific B cells and to lower serum concentrations of HBV DNA and HBsAg. ASC22 (Envafolimab) is a single-domain antibody formed by fusing a PD-L1 domain with Fc fragments of a human IgG1 antibody. It exhibits strong binding to PD-1, thereby blocking PD-1 signaling and enhancing T-cell function. Nivolumab, an IgG4 monoclonal antibody, targets PD-1, blocking its interaction with PD-L1 and restoring T-cell activity. The FDA has approved nivolumab for the treatment of advanced hepatocellular carcinoma (HCC) following sorafenib therapy, and it is also applicable in adult CHB patients.[14]

Blocking PD-1 signaling in CD8+ T cells, when combined with entecavir treatment and DNA-based vaccination, can significantly improve the functionality of virus-specific T cells. Overall, PD-1 inhibitors represent a promising therapeutic option for CHB. Despite the potential drawbacks of PD-1 blockade—such as promoting T-cell aging, triggering other inhibitory pathways, causing liver cell damage, or reactivating dormant hepatitis viruses—its combination with other treatments can enhance the overall effectiveness of CHB therapy.[14]

CTLA-4 inhibitors

CTLA-4 inhibitors have demonstrated various effects on T cells and the immune response. They can either deplete regulatory T cells (Tregs) or suppress their function, restore the activity of T follicular helper cells in response to HBsAg, and support the elimination of HBV. These inhibitors also enhance the proliferation of HBV-specific CD8+ T cells and increase IFN-γ production.[14]

Other immune checkpoint inhibitors (ICIs)

Other ICIs show promise as well. For instance, blocking TIM-3 leads to a significant rise in CD8+ T-cell proliferation and antiviral cytokine secretion, thereby reducing HBV replication. Additionally, antiviral therapies have been found to suppress TIM-3 expression on T cells in individuals infected with HBV. Inhibiting TIM-3 also reduces HBV replication through α-GalCer and lowers levels of HBV DNA and HBsAg in the blood. One advantage of TIM-3 inhibitors over other ICIs is that TIM-3 is only expressed during the terminal differentiation stage of IFN-producing T cells, whereas CTLA-4 and PD-1 are found on all activated T cells. This makes TIM-3 inhibitors less likely to cause cytotoxic side effects. Another advantage is that, while TIM-3 inhibitors alone do not yield significant clinical benefits, they are typically used in combination with other therapies for treating chronic hepatitis B (CHB).[14]

CLINICAL TRIAL

In a study by Kothapalli and Khattak involving seven patients with chronic or past HBV/HCV infection who were treated with PD-1 inhibitors for metastatic melanoma or metastatic non-small cell lung cancer, patients with chronic HBV infection were maintained on concurrent nucleoside analogue (NUC) therapy during anti–PD-1 treatment. In contrast, those with resolved infection did not require antiviral therapy. Two patients showed no signs of liver toxicity and maintained stable disease after receiving more than 24 cycles of nivolumab.[22] Additionally, the study by El-Khoueiry et al., a multicenter, open-label, non-comparative phase 1/2 study evaluating nivolumab in patients with advanced hepatocellular carcinoma, required patients with chronic HBV infection to be on effective antiviral therapy (NUCs) and to have controlled viral replication prior to enrollment; antiviral therapy was continued throughout the study period. Among the 48 participants in the dose-escalation phase, 12 experienced grade 3 or

4 treatment-related adverse events, and three developed serious treatment-related complications, including herpes, adrenal insufficiency, and liver disease. These findings suggest that nivolumab may be a viable and relatively safe option for patients with chronic hepatitis B when administered in the context of appropriate antiviral suppression with NUCs; however, further research is needed to determine its effectiveness as a stand-alone therapy.[23]

Checkpoint inhibitors have transformed cancer therapy and may also help reestablish immune control over HBV. In the randomized phase 2b study by Qian et al., evaluating the subcutaneous PD-L1 antibody ASC22 (Envafolimab) in virally suppressed HBeAg-negative chronic hepatitis B patients, all participants were required to be on stable background NUC therapy with sustained viral suppression prior to randomization and continued antiviral treatment during the trial. HBsAg loss was observed in 3 out of 10 participants receiving 1.0 mg/kg ASC22 after 24 weeks of treatment, although all had baseline HBsAg levels below 100 IU/mL.[24]

Previous efforts using therapeutic vaccines have failed to achieve clinical effectiveness in both virally suppressed and NUC-naïve patients, despite enhancing cytokine production and HBV-specific immune responses. As discussed by Gehring et al., most immunotherapeutic cure strategies are currently being developed as add-on approaches to ongoing NUC therapy rather than as NUC-free regimens, given the importance of maintaining viral suppression to reduce antigen load and immune exhaustion.[25] In a phase 2b, open-label study conducted by Sorensen et al., VTP-300, a therapeutic prime-boost regimen consisting of ChAdOx1-HBV and MVA-HBV vectors encoding multiple HBV antigens, was evaluated in combination with low-dose nivolumab in patients with chronic hepatitis B infection. Eligible participants were required to be on long-term suppressive nucleos(t)ide analogue (NUC) therapy with sustained viral suppression prior to enrollment, and background antiviral treatment was maintained throughout the study period. The study assessed multiple treatment regimens to evaluate efficacy, safety, tolerability, and immunogenicity. Sustained reductions in HBsAg levels were observed, particularly among patients with low baseline HBsAg levels (<200 IU/mL); however, functional cure (defined as durable HBsAg loss off therapy) was not achieved. These findings further support the concept that therapeutic vaccination combined with immune checkpoint inhibition may enhance HBV-specific immune responses. Still, current evidence suggests that such strategies remain adjunctive to, rather than replacements for, ongoing NUC therapy.[26] The summary of its clinical trial is shown in **Table 1.**

POTENTIAL SIDE EFFECTS

Immune checkpoint inhibitors (ICIs), particularly those targeting the PD-1/PD-L1 axis, exert complex and seemingly paradoxical effects in chronic hepatitis B infection. On one hand, chronic HBV infection is characterized by functional exhaustion of HBV-specific $CD8^+$ T cells, mediated in part through sustained PD-1 signaling. Blockade of PD-1/PD-L1 can partially restore antiviral T-cell function, enhance cytokine production (e.g., IFN-γ, TNF-α), and promote cytolytic activity against infected hepatocytes. This immunological reinvigoration provides the mechanistic rationale for using ICIs as a potential strategy to reduce HBsAg levels and facilitate immune-mediated viral control. However, the same immune reactivation may destabilize the delicate equilibrium between viral replication and host immune tolerance that exists in chronic HBV infection. As described by Inoue et al., Godbert et al., and Lombardi & Mondelli, abrupt restoration of T-cell activity can lead to a rapid increase in immune-mediated hepatocyte destruction, resulting in hepatitis flares and clinical HBV reactivation.[27–29]

In HBsAg-positive patients, especially those not receiving nucleos(t)ide analogue (NUC) therapy, immune checkpoint blockade may permit increased immune-mediated cytotoxicity without adequate suppression of viral replication, thereby exacerbating hepatic inflammation. Furthermore, ICIs can alter regulatory T-cell function and intrahepatic immune homeostasis. Disruption of these regulatory pathways may transiently increase viral transcription or unmask occult HBV infection, particularly in patients with resolved infection (HBsAg-negative, anti-HBc-positive), where covalently closed circular DNA (cccDNA) persists in hepatocytes. In this context, viral replication may rebound under immune perturbation, clinically manifesting as HBV reactivation. Reactivation of HBV in patients undergoing treatment with ICIs has been well-documented. Inoue et al. highlight that patients who are positive for hepatitis B surface antigen (HBsAg) and are treated with ICIs are at significant risk of experiencing severe HBV reactivation and recommend prophylactic treatment with antiviral agents such as nucleos(t)ide analogues.[27]

Table 1. Summary of Clinical Trials Involving Immune Checkpoint Inhibitors (ICIs) in Hepatitis B Context

Type of ICI	Number of Patients	Study design	Population	NUC Treatment	Main Outcome	Adverse Effect
Nivolumab, Pembrolizumab (PD-1 inhibitors)[22]	7	Case series in cancer patients with chronic/past HBV/HCV	Mixed population: chronic HBV (HBsAg+), past HBV (HBsAg−/anti-HBc+), and HCV. HBV DNA levels controlled in chronic cases; viral load not high at baseline.	Chronic HBV patients received antiviral prophylaxis (NUC); resolved HBV cases did not require NUC.	Two patients remained stable after >24 cycles of nivolumab with no liver toxicity.	One patient showed an increase in ALT of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 severity. Four patients showed an increase in ALT of CTCAE grade 1 severity.
Nivolumab (PD-1 inhibitor)[23]	262	Multicenter, non-comparative, open-label Phase 1/2 trial	Advanced HCC; included HBV-infected patients (HBsAg+). Required controlled HBV DNA (<100 IU/mL) prior to enrollment.	HBV patients required ongoing antiviral therapy (NUC) before and during study.	Nivolumab was found to be relatively safe and potentially effective in HBV patients.	Three (6%) patients had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder).
Nivolumab ± GS-4774 (therapeutic vaccine)[20]	24	Phase 1b trial in virally suppressed CHB patients	All patients HBsAg+ CHB; virally suppressed (HBV DNA undetectable or low) on therapy prior to enrollment.	All participants maintained on stable NUC therapy throughout study.	One patient (4.5%) achieved sustained HBsAg loss 12 months post-treatment	Most AEs were grade 1 in severity (fatigue, headache, cough)
Envafolimab (ASC22), a humanized PD-L1 monoclonal antibody	149	Randomized Phase 2b trial in HBeAg-negative, virally suppressed CHB	All HBsAg+; HBeAg-negative; virally suppressed on NUC; baseline quantitative HBsAg required, response observed mainly in patients with HBsAg <100 IU/mL.	All patients on stable background NUC therapy.	HBsAg loss in 3/10 patients receiving ASC22 1.0 mg/kg subcutaneously every 2 weeks for 24 weeks (responders had HBsAg <100 IU/mL at baseline).	Most adverse events were mild (97.9%).
Low-dose Nivolumab (PD-1 inhibitor)[26]	74	Phase 2b trial using prime-boost vaccine with PD-1 blockade	CHB patients; HBsAg+; required low baseline HBsAg (<200 IU/mL in responsive subgroup); HBV DNA suppressed prior to enrollment.	All patients maintained on long-term suppressive NUC therapy.	Reduction in HBsAg levels in patients with <200 IU/mL HBsAg; no functional cure observed	Not reported

A systematic review by Lombardi and Mondelli notes that these side effects, including reactive hepatitis, can originate from the immune mobilization triggered by checkpoint inhibition, the very mechanism that makes these agents effective against tumors.[29]

The challenge of managing HBV reactivation during ICI therapy is heightened by the frequent use of ICIs in patients with various malignancies, many of whom may already have chronic liver conditions. Immune-mediated liver injury is a substantial risk during ICI treatment, and underlying viral hepatitis complicates the diagnosis and management of immune-related liver injuries.[28,30] For example, Godbert et al. emphasize that immune-mediated liver injury is a significant risk during ICI treatment, where the presence of underlying viral hepatitis can complicate the diagnosis and management of immune-related liver injuries. They advise that supportive care and vigilant monitoring should be instrumental in mitigating the risks associated with these adverse events in at-risk populations.[28,31]

Moreover, the type of ICI administered also plays a critical role in the risk profile for HBV reactivation. Cao et al. highlight that various immunosuppressive or cytotoxic agents carry differing levels of risk for HBV reactivation, underscoring the need for careful screening of HBV status before initiating ICI therapy.[32] Specifically, the likelihood of reactivation is particularly notable in conjunction with certain therapies that include B-cell depleting antibodies and high-dose corticosteroids.[31,32] Furthermore, research emphasizes the importance of recognizing the potential for HBV reactivation not just among patients currently undergoing chemotherapy but also among those whose immune system has been compromised previously by viral infections.[28,32] Interestingly, some studies indicate that while concomitant viral infections like HBV do not significantly influence the overall toxicity and efficacy of ICIs, the potential for viral reactivation remains a major concern due to unpredictable immune responses during therapy.[28,31] This is reflected in case studies where patients experienced fatal outcomes post-ICI treatment due to uncontrolled HBV reactivation, underscoring the need for immediate and proactive management strategies.[33]

FUTURE DIRECTION

The persistence of covalently closed circular DNA (cccDNA) in hepatocytes is a key factor in maintaining chronic HBV infection, making accurate detection and quantification of cccDNA essential for assessing true viral eradication. Quantitative HBsAg has become the most commonly used and widely accessible biomarker for this purpose. After years of limited progress in CHB therapy, a variety of novel agents, either as monotherapies or in combination, are now emerging as promising treatment options.[34] Among the most promising strategies is the use of immune checkpoint inhibitors (ICIs), which have already revolutionized cancer immunotherapy. In chronic HBV infection, prolonged viral antigen exposure leads to T cell exhaustion, characterized by impaired antiviral activity and the upregulation of inhibitory receptors like PD-1, CTLA-4, TIM-3, and LAG-3. Immune checkpoint blockade, particularly targeting the PD-1/PD-L1 axis, offers a strategy to restore HBV-specific T cell responses and potentially regain immune control over the virus. Preliminary clinical trials have shown that ICIs such as nivolumab, pembrolizumab, and envafolimab may enhance immune responses in HBV-infected individuals, especially when combined with other therapies like therapeutic vaccines, siRNA agents targeting HBV transcripts, and nucleoside analogs (NUCs). Early-phase studies have shown HBsAg decline or loss, particularly in patients with low baseline levels, though consistent functional cures have not yet been achieved. While ICIs alone may not be a stand-alone cure for hepatitis B, their role in multimodal immunotherapy regimens holds increasing promise. With continued clinical investigation and refinement, immune checkpoint blockade could become a cornerstone of future HBV cure strategies.[14,21,24,26,34]

The highest-yield candidates for ICI-augmented functional-cure strategies may be (i) CHB patients on long-term NUC therapy with undetectable/low HBV DNA but persistent HBsAg, particularly those with lower baseline HBsAg, suggesting reduced antigenic pressure and less profound T-cell exhaustion; (ii) individuals with compensated liver disease (no decompensation) to reduce the risk of severe hepatitis flares; and (iii) HBV-infected patients already receiving ICIs for HBV-related HCC or other malignancies, where close monitoring can generate pragmatic insights on safety and virologic/serologic changes. Conversely, patients with decompensated cirrhosis, uncontrolled autoimmune disease, or transplant-related immunosuppression should generally be restricted to carefully designed trials due to higher immune-related risk.

A rational near-term roadmap is a NUC backbone (to suppress replication and reduce flare risk) plus siRNA-based antigen knockdown (to decrease HBsAg and other viral proteins that perpetuate immune exhaustion), followed by therapeutic vaccination (to re-prime HBV-specific T-cell responses) and then PD-1/PD-L1 blockade as a "checkpoint release" step to sustain effector function. This sequential, multimodal approach aligns mechanism with risk mitigation, antigen reduction may increase vaccine immunogenicity, and potentially allow more conservative ICI exposure.

CONCLUSION

In conclusion, effective treatment for hepatitis B could have a major impact on reducing global mortality, and the use of ICIs offers hope as a new treatment pathway. However, ICIs are still not fully understood, including their safety and efficacy, which still need further investigation. To maximize benefits and reduce risks, ICIs should be used in combination with other therapies. ICIs should not be framed as a stand-alone cure strategy for CHB; rather, they are best positioned as an adjunct to restore HBV-specific immunity once viral replication and antigen load have been reduced. A NUC backbone remains non-negotiable in most combination strategies to minimize virologic rebound during immune reactivation. The near-term value proposition of ICIs lies in carefully selected patients and sequential, multimodal regimens with stringent safety monitoring.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

All authors contributed equally in preparing this manuscript.

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