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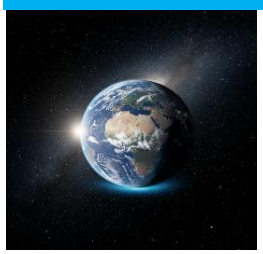

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Recent Developments in Hepatitis B Treatment - A Review

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Abstract

Background

Hepatitis B remains a global health concern, despite programs aimed at reducing its prevalence. Current mainline treatments are largely successful in reducing infection symptoms; however, viral reservoirs continue to pose a barrier to achieving a functional cure.

Aim

This review aims to highlight emerging options for HBV treatment to inform physicians and other medical professionals of the potential methods of potentizing antiviral therapies, preventing infections, and achieving seroclearance that might become available in the coming years.

Materials and Methods

The article provides a review of studies and trials showcasing novel HBV treatment alternatives, limiting its scope, when possible, to the past 5 years of results in order to maximize relevancy. Publications available in the PubMed and Google Scholar databases were included, among others. The literature review and article selection process concluded in February 2026.

Results

The available studies show that NTCP inhibitors, such as Bulevirtide, display a well-established effect in preventing viral entry. In limited-scope trials, a combination of capsid assembly modulator Morphotiandin and ritonavir showed greater efficacy than a ritonavir monotherapy. cccDNA elimination via HDAC11 overexpression, targeting by specific xanthone derivatives, and methods of viral genome editing offer a possibility of eliminating viral reservoirs; however, their safety and specificity must be further researched before clinical application. Trials involving immunomodulatory agents and small-interfering RNA have resulted in notably higher rates of seroclearance than control groups.

Conclusions

While, with the exception of Bulevirtide, the showcased treatments are not yet available on the market, they may eventually be regarded as a significant tool in combating infections at various points of the viral life cycle. The above-mentioned methods, particularly those focusing on cccDNA elimination and RNA interference, as well as immunomodulatory agents, have shown a considerable potential in achieving the long-sought therapeutic benchmark of a functional cure, i.e., a sustained loss of hepatitis B surface antigen (HBsAg), with or without anti-HBs seroconversion, after completion of therapy.

Keywords: hepatitis B, HBV, cccDNA, antiviral treatment

Introduction

Despite the adoption of a global health sector strategy by the World Health Assembly nearly a decade ago [1], viral hepatitis continues to affect a substantial proportion of the overall population. Current epidemiological models estimate an overall prevalence of 3.2%, which corresponds to approximately 257.5 million individuals living with the infection, of which fewer than 6.8% are receiving treatment. Prophylactic interventions, such as vaccination, have reduced the prevalence among children within the 0-5 age range to 0.7% [2], and improved screening and treatment programs have enabled even lower rates in developed countries, such as 0.5% in the European Economic Area [3]. Nevertheless, HBV remains a common cause of fatigue, nausea, jaundice, and abdominal pain, and in the nearly 20% of patients, particularly neonates and the elderly, who develop a chronic infection [4], it can lead to liver cirrhosis and cancer.

Clinical recommendations issued by the European Association for the Study of the Liver indicate that antiviral therapy should be administered to patients with HBV DNA levels exceeding 2,000 IU/ml, elevated alanine aminotransferase (ALT) and/or at least moderate histological lesions, as well as all patients with cirrhosis and detectable HBV DNA. [5]. Additional indications include the prevention of vertical transmissions in pregnant women with high viremia, as well as the prevention of HBV reactivation in patients undergoing immunosuppression or chemotherapy [5].

The American Association for the Study of Liver Diseases further clarifies the clinical criteria for antiviral treatment, outlining tenofovir, entecavir, and pegylated interferon (Peg-IFN) as the preferred initial treatment for adults with chronic Hepatitis B [6]. In the current guidelines, the routine use of combination regimens is generally discouraged. Data from extended follow-up studies show that nucleoside analogues, particularly tenofovir and entecavir, achieve sustained

virological suppression in approximately 95% of treated patients [7], with low rates of resistance and favorable safety profiles. Nevertheless, their usage remains limited by their potential for nephrotoxicity, reductions in bone mineral density, and possible interactions with other medications affecting renal function [8].

Current research on HBV treatment primarily aims to enhance effectiveness by targeting various stages of the viral life cycle, eliminating persistent reservoirs, addressing co-infections, and achieving a functional cure. This review aims to briefly summarize those efforts in order to inform medical professionals of the emerging possibilities.

Entry Inhibitors

A pivotal step in HBV infection is the virus's entry into hepatocytes. This process is mediated by the interaction between the hepatitis B surface antigen (HBsAg) and the sodium taurocholate co-transporting polypeptide (NTCP) - a bile acid transporter located on the hepatocyte surface. It has been shown that silencing NTCP inhibits HBV and HDV infection, while exogenous NTCP expression renders non-susceptible hepatocarcinoma cells susceptible to these viral infections, proving it to be the functional receptor for these viruses [9]. Further studies have shown that the bile acid derivative INT-767 preferentially binds to the HBV preS1 region, which mediates the virus's binding to NTCP, providing an additional potential mechanism to prevent HBV entry [10]. Another treatment avenue might present itself with neuropilin-1 inhibition. Mechanistic studies indicated that NRP1 formed a complex with LHBs (large hepatitis B surface proteins) and NTCP. This NRP1-preS1 interaction subsequently promoted preS1 binding to NTCP, thereby facilitating viral infection. Moreover, disruption of the NRP1-preS1 interaction by the NRP1 antagonist EG00229 significantly attenuated the binding affinity between NTCP and preS1, thereby inhibiting HBV infection both in vitro and in vivo [11]. However, as of yet, research into these, as well as several other pathways of blocking HBV entry, remains in the early stages, and some time may pass before entry inhibitors become available for clinical usage.

So far, bulevirtide is the only entry inhibitor available on the market, approved for medical use within the European Union in July 2020 [12]; however, only for the treatment of HDV co-infections. The molecule functions by binding directly to NTCP, forming a complex that inhibits NTCP's physiological function and prevents viral entry into the cell [13]. When used as HBV treatment, patients receiving a bulevirtide monotherapy demonstrated a markedly

higher combined virological and biochemical response - 45% for the 2 mg dose and 48% for the 10 mg dose, after 48 weeks of therapy, compared with only 2% of those who did not receive antiviral treatment. [14]. In the further 96-week follow-up, efficacy responses were maintained and/or improved from W48 to W96, with similar combined, virologic, and biochemical response rates for both doses. Among patients with a suboptimal early virologic response at W24, 43% of non-responders and 82% of partial responders achieved virologic response at W96 [15]. Promising results have also been shown by rapavir, a synthetic analog of the HP07-C6 rapafucin – a macromolecule inspired by the natural products rapamycin and FK506, with a potent inhibitory effect on NTCP [16].

Capsid Assembly Modulators

Capsid assembly modulators (CAMs) are a novel group of molecules targeting the core protein, a building block of the HBV nucleocapsid. Specifically, structural studies show that CAMs bind to a hydrophobic pocket located at the core dimerization interface of the core assembly subunits, close to their C-termini. Filling this pocket by CAMs causes structural changes in the core dimer, severely impairing correct capsid assembly and, thus, blocking the internalization of the pgRNA-polymerase and reverse transcription. The result, depending on the chemotype used during treatment, is the formation of core aggregates, aberrant, or normal nucleocapsids devoid of the pgRNA-polymerase complex [17].

Several capsid assembly modulators have entered clinical trials. Results of the phase-2 JADE study on Bersacapavir (JNJ-56136379) show that, when used in tandem with a nucleoside analogue on patients with non-cirrhotic chronic Hepatitis B the molecule achieved pronounced reductions in HBV DNA and RNA, limited HBsAg or HBeAg declines in patients who are HBeAg positive, and was well tolerated, yet no clear benefit regarding their efficacy over standard nucleoside analogues was observed [18]. Morphotiandin (GLS4) – a heteroaryldihydropyrimidine derivative, has shown activity against various polymerase drug-resistant strains, including those resistant to nucleoside analogues. A study was conducted to evaluate the effectiveness and safety of a GLS4/ritonavir combination together with entecavir compared to entecavir alone in individuals with chronic hepatitis B who are HBeAg-positive. In said study, in the mid-term, significantly higher fractions of HBV DNA and pgRNA-negative patients were reached, both in the treatment-naïve cohort (17.3% v 0%) and among those who had previously achieved viral suppression (71.6% v 18.9%), when GLS4-

based polytherapy was administered [19]. A phase IIIa clinical trial of morphotiandin is currently ongoing (CTR20213273), though official results have not yet been published.

Elimination of cccDNA

A major obstacle to achieving complete viral clearance in patients with chronic hepatitis B is the continued presence of covalently closed circular DNA (cccDNA) within infected hepatocytes. Due to the importance of this factor in achieving a functional cure, numerous strategies are currently being developed to combat cccDNA persistence [20]. A few years ago, it was found that histone deacetylase 11 (HDAC11) specifically reduces the acetylation of cccDNA-bound histone H3, and that its overexpression additionally decreases the levels of cccDNA-bound acetylated H3K9 (H3K9ac) and H3K27 (H3K27ac), which allowed for the restriction of HBV replication through the epigenetic repression of cccDNA transcription [21]. Furthermore, several small molecules, primarily xanthone derivatives, have shown potential in eliminating cccDNA. Among those, ccc_R08 resulted in notably lower HBV DNA, HBsAg, and HBeAg levels, as well as a selective reduction of cccDNA, without clear cytotoxicity. However, further studies are required to assess its safety and to clarify whether ccc_R08 targets cccDNA directly, as its mechanism remains largely uncertain [22]. Another promising compound – PAC5, an agonist of hnRNPA2B1 - when administered orally in mouse models, eliminated HBV cccDNA and reduced the large antigen load by leading to an extensive production of type I interferon with antiviral activity [23]. Genome editing offers yet another possibility for combating cccDNA. The CRISPR/Cas9 expression vector, delivered by the method of hydrodynamic injection, has shown the ability to accurately target HBV cccDNA and inhibit HBV replication. Before CRISPR-Cas9 can be applied in clinical settings, however, it must be ensured that the guide RNA designed for cccDNA targets only the intended sequence, without binding to the host's own DNA [24].

Immunomodulatory Treatments

Numerous agents are currently being developed that suppress HBV infection by modulating the patient's immune responses. Toll-like receptor agonists, such as selgantolimod, induce the production of interleukins (IL-12 and IL-18) as well as tumor necrosis factor (TNF)-α and interferon (IFN)-γ. Additionally, they play a role in activating natural killer (NK) cells and

mucosal-associated invariant T cells, and in stimulating CD8+ T-cell proliferation. In a study evaluating their efficacy, after 48 weeks of monotherapy, 10/39 patients treated with the TLR-8 agonist experienced HBsAg declines greater than 0.1 log10 IU/ml, with HBsAg seroclearance in 2/39 cases [25].

Another available angle of approach is the suppression of co-stimulatory molecules PD-1 (Programmed cell death protein-1) and PD-L1 (PD-ligand 1), which inhibit a patient's immune response. Hampering the PD-1/PD-L1 interaction has led to in vitro improvements in HBV-specific T-cell function and increased T-cell proliferation. Promising results have been reported with subcutaneous administration of ASC22 (envafolimab), a humanized, single-domain programmed cell death ligand 1 antibody. In a cohort with baseline qHBsAg <100 IU/mL, 24-week treatment with envafolimab led to >1 log reduction in qHBsAg in 42.1% of patients, with 21.1% achieving HBsAg seroclearance [26].

Additionally, humoral immunity may be induced by monoclonal antibodies. VIR-3434 is an anti-HBV monoclonal antibody that induced a mean HBsAg and HBV DNA reduction by 1.83 and 2.03 log after a single infusion, respectively. Preliminary data showed that even a single low dose (6 mg) of VIR-3434 in patients with chronic hepatitis B produced rapid HBsAg reduction, which was maintained for two weeks after administration [27].

RNA interference

Another approach explored in recent years for treating HBV involves the use of small-interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), which affect post-transcriptional messenger and pregenomic RNAs, leading to the decreased production of HBV antigens and the suppression of viral replication. Administered once per month, it has shown potential to achieve a sustainable, dose-dependent mean HBsAg reduction of 2-2.5 log [28]. The recent results of a phase 2 study involving elebsiran further support its effectiveness. When used in combination with weekly PEG-IFNα treatments for 48 weeks, HBsAg loss was achieved in 21.1% of participants receiving 200mg of elebsiran and 33.3% of those receiving 100mg, compared with 5.6% of participants receiving a PEG-IFNα monotherapy [29]. Several other siRNAs are currently in clinical trials, such as imdusiran, which, in mouse models, achieved HBsAg reductions up to 3.7 log after a single dose, with sustained suppression for 10 weeks [30].

Conclusions

Except for Bulevirtide, the treatments discussed are not yet commercially available, but they may become important tools for targeting infections at multiple stages of the viral life cycle. Importantly, approaches aimed at eliminating cccDNA, including RNA interference and immunomodulatory compounds, have shown substantial promise in achieving the therapeutic goal of a functional cure, characterized by a lasting disappearance of hepatitis B surface antigen (HBsAg), with or without subsequent anti-HBs seroconversion after treatment completion.

DISCLOSURES

Author's contribution:

Conceptualization: PG, MC, JM

Methodology: PG, MC, JM

Formal analysis: PG, MC, JM

Investigation: PG, MC, JM

Writing - rough preparation: PG, MC, JM

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