

Therapeutic Options against Chronic HBV

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Definition

Currently, Chronic Hepatitis B (CHB) is controlled but not cured by approved antivirals. For instance, transcriptionally active HBV DNA in the nucleus is not directly targeted. Except for interferon- α (IFN- α) and pegylated IFN- α , all other licensed drugs are nucleoside (Lamivudine, Clevudine, Entecavir, Telbivudine) and nucleotide analogues (Adefovir dipivoxil, Tenofovir disoproxil fumarate, Tenofovir alafenamide). All these drugs are potent at reducing viral loads and normalizing alanine transaminase levels in CHB patients. However, long-term treatment with many of these drugs leads to the development of multiple drug resistance mutations. In addition, while a limited reduction in cccDNA is achieved, long-term nucleos(t)ide analogue treatment does not reduce hepatitis B surface antigen (HBsAg) levels.

1. Introduction

In the past decade, global deaths from viral hepatitis have increased to become the seventh leading cause of mortality, annually causing more deaths than AIDS, diabetes, and tuberculosis (1.4 million/year) [1]. Viral hepatitis results in liver inflammation and is caused by hepatotropic viruses, with both acute or chronic disease courses described. These liver-tropic pathogens represent a range of DNA and RNA viruses from diverse viral families with distinct modes of transmission: Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis delta virus (HDV), and Hepatitis E virus (HEV). Both HCV and HBV can cause chronic infections in immune-competent individuals [2], potentially leading to progressive liver injury. According to the World Health Organization, HBV and HCV chronically infect 240 million and 71 million people, respectively. Chronic infections may ultimately result in liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Indeed, an estimated 75% of all HCC cases are attributed to chronic infection with HBV (CHB) or HCV [3,4].

2. Approved Drugs and Potential Therapeutic Options against Chronic Hepatitis B

Both virus and host druggable targets exist at multiple stages of the HBV life cycle, including viral entry, replication, assembly, and the secretion of subviral particles [1].

Myristoylated preS1-derived lipopeptide (Myrcludex B) specifically bound to the human sodium taurocholate co-transporting polypeptide (hNTCP), the bona fide HBV and HDV receptor, prevents HBV entry in urokinase-type plasminogen activator and severe immunodeficient (uPA-SCID) mice repopulated with primary human hepatocytes [2]. Myrcludex B also potently blocked HBV spreading from initially infected hepatocytes to uninfected cells [3]. Although HBsAg levels remained, HBV viral load was significantly decreased at week 24 in the pegylated IFN- α -Myrcludex B cohort (n = 7) compared with Myrcludex B monotherapy (n = 8) in a phase 1b/IIa trial [4].

For HBV replication, the RNase H domain within viral polymerase has also been effectively targeted by specific inhibitors in previous preclinical trials [5][6][7].

The availability of high-resolution structures for HBV nucleocapsids has facilitated the development of multiple capsid allosteric modulators [8][9][10]. Recently, one leading compound, NVR 3-778, showed reduced HBV DNA and RNA levels in patient serum (n = 43) when administered as monotherapy, with a larger reduction observed in combination with pegylated IFN- α (n = 10) [11]. Morphothiadin (GLS4), a derivative of heteroaryldihydropyrimidine targeting capsid maturation, showed a potent in vitro antiviral activity and tolerability in healthy participants (n = 8) when co-administered with Ritonavir, which

boosted plasma concentrations of morphothiadin [12]. More recently, JNJ-56136379 (JNJ-6379) showed good tolerability in treatment-naïve chronic HBV patients in a phase I study. Remarkably, 32% of patients (13/41) had undetectable HBV DNA levels at 4 weeks treatment, despite no alteration in HBsAg levels [13]. In another trial, ABI-H0731 showed safety at 300 mg/day but non-specific side effects at higher doses in some participants. The treatment resulted in dose-dependent declines in both HBV DNA and RNA levels [14].

Two nucleic acid polymers were shown to inhibit the secretion of subviral particles. Both REP 2139 and REP 2165 were well tolerated and showed a substantial activity in treatment-naive patients. The combination of Tenovofir, pegylated IFN- α , and REP promoted HBsAg seroconversion (<0.05 IU/mL) in 60% of patients (24/40). During 48 weeks of follow-up, no viral rebound was observed in 35% of patients (14/40) [15].

All lines of evidence detailed above demonstrate that HBV replication can be controlled, but a permanent cure has not been achieved. Notably, none of the above drugs (except IFN- α) target transcriptionally active templates and decompose viral transcripts. Thus, transcriptionally active templates should be recognized as novel drug targets, and any new-class antivirals targeting this virus life-cycle stage could represent a potential therapeutic option against CHB.

Indeed, taking advantage of authentic infection models that allow cccDNA-mediated replication, a number of candidates were identified that either inhibit transcription or impact on the stability of existing viral transcripts [16].

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Keywords

Chronic Hepatitis B;Therapeutics;Drug Development

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