Treatment of Chronic Hepatitis B

Subjects: Virology

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Chronic carriers of hepatitis B virus (HBV) run the risk of developing cirrhosis and hepatocellular carcinoma over time. Antiviral treatment offers the only means of arresting this process. Treatment relies on the use of an immune modulator such as pegylated interferon alpha (Peg-IFN-a) for a finite time or nucleosi(t)ide analogues which target the reverse transcriptase/DNA polymerase and can be used long-term. Drugs in development which target stages in the life cycle of the virus are reviewed, as are any results from their preclinical or clinical evaluation.

Keywords: Hepatitis B virus ; Chronic hepatitis ; Cirrhosis ; Hepatocellular carcinoma ; Antiviral agents ; cccDNA ; Viral replication ; Nucleos(t)ide analogues ; Pegylated interferon

1. Introduction

Hepatitis B virus (HBV) is a major public health threat worldwide as nearly 300 million individuals have chronic HBV infection. These patients are at lifelong risk of developing liver cirrhosis and hepatocellular carcinoma (HCC). Currently, two classes of therapeutic agents are approved for the treatment of chronic HBV infection, which can interrupt or prevent this undesirable progression, i.e., the nucleos(t)ide analogues (NAs) and pegylated interferon alpha (Peg-IFN-a). However, both have limitations. On the one hand, the nucleos(t)ide analogues are oral, second generation, reverse transcriptase inhibitors including tenofovir disoproxil fumarate (TDF), entecavir, and the recently approved tenofovir alafenamide (TAF). They effectively suppress HBV DNA levels and have been demonstrated to prevent disease progression to cirrhosis, reverse liver fibrosis, and even cirrhosis, and to reduce but not eliminate, the risk for HCC [1]. However, NAs have little effect on the covalently closed circular DNA (cccDNA), the stable episomal form of the HBV genome which has a very long half-life and can persist for decades in hepatocytes despite effective viral suppression [2]. Hence, NAs do not lead to HBsAg loss, but only to the suppression of viral replication requiring prolonged treatment (indefinite) with concomitant costs [3]. On the other hand, Peg-IFN-a treatment is for a limited period and acts on different phases of the HBV life circle. However, it has a low response rate and the drug is difficult to tolerate [1].

The optimal goal of chronic HBV infection treatment is to attain a “functional cure” of the disease defined by loss of hepatitis B surface antigen (HBsAg) preferably with development of anti-HBs, which results in undetectable HBV DNA in the serum, normalization of liver enzymes, and improved liver histology after treatment cessation [2]. However, in chronically HBV-infected patients, the frequency with which NAs induce HBsAg loss is negligible, particularly in HBeAg-negative patients. Discontinuation of NAs, after a long period of persistent viral suppression, has recently been suggested by the European Association for the Study of the Liver (EASL) [1]. However, according to recent investigations [4], the monitoring of early treatment-free follow-up was demanding and almost half of these patients were not compliant with the requirements. Safety issues were raised in the early treatment-free period due to the possibility of developing acute-on chronic HBV infection, thus one must ensure that the hepatocyte reservoir is at adequate levels. In addition, only a minority of those who stopped NAs, achieved HBsAg loss [4].

It is critical, therefore, to develop new antiviral treatments capable of achieving a functional cure of the disease, and thus reducing the risk of HBV-induced HCC. Ideally, such treatments need to be administered for a finite period of time and at a reasonable cost. Major advances have been made towards understanding multiple steps of the viral life cycle and the mechanisms involved in the evasion of host immune responses that allow the establishment of persistent infection.

2. HBV Structure and Genomic Organization

Three types of viral particles are present in the serum of an infected individual visible by electron microscopy, i.e., the complete infectious virion or Dane particle and two types of subviral particles known as spheres and filaments [5]. The Dane particle is a spherical particle measuring 42 nm in diameter and consists of an outer envelope made of HBsAg in a lipid bilayer [6]. This encloses the nucleocapsid core of the virus, which in turn contains a single copy of the viral genome

covalently linked to the terminal protein of the virus [7]. There is an abundance of subviral particles, which outnumber infectious virions by 100- to 10,000-fold and are exclusively composed of HBs proteins and host derived lipids, lacking any nucleic acid containing cores [8].

The 3.2 kilobases (kb) in length circular partially double-stranded HBV DNA genome contains the four open reading frames (ORFs) of the virus which are the surface (PreS/S), core (C), polymerase (P) and X. These encode a total of seven proteins translated from six co-terminal, unspliced and capped mRNAs ending at a common polyadenylation signal, which is situated in the core ORF. Regulatory elements such as the two enhancers (Enh1 and Enh2), the four promoters (core, S1, S2, and X), the polyadenylation, encapsidation (epsilon), and replication (DR1, DR2) signals are situated within these ORFs and direct the synthesis of the mRNA transcripts through the recruitment of transcription factors which are particularly enriched in hepatocytes [5].

Transcription of the cccDNA occurs in the hepatocyte nucleus [8]. The core promoter is responsible for the synthesis of two longer than genome length mRNAs (3.5 kb), which differ with respect to the start of their 5′ end. The precore mRNA is the longer of the two by a small number of ribonucleotides and contains the initiation codon for synthesis of the precore protein. This is the precursor for provision of the hepatitis B e antigen (HBeAg) following proteolytic processing. The HBeAg is thought to have an immunoregulatory role that facilitates chronic infection establishment and is an important marker of active viral replication [5]. The other transcript is bicistronic and encodes for the core protein (21kD) or hepatitis B core antigen (HBcAg) and the viral polymerase (90kD). It is known as the pregenomic RNA (pgRNA). The core dimerises spontaneously and can form nucleocapsids by self-assembly consisting of 240 copies (120 dimers) of the protein [9]. The polymerase is a multifunctional protein which fulfils a number of roles such as in the facilitation of DNA synthesis during the replication process, reverse transcription, and degradation of the pgRNA. Synthesis of these two proteins is regulated in such a way as to favor the generation of the core molecules required for nucleocapsid formation per single molecule of polymerase packaged with the pgRNA [5].

The S ORF contains three in frame start (ATG) codons that divide the gene into three sections, pre-S1, pre-S2, and S. Thus, polypeptides of three different sizes known as large (L-HBsAg)(pre-S1 + pre-S2 + S), middle (M-HBsAg)(pre-S2 + S), and small (S-HBsAg) are produced [10]. Two transcripts of 2.4 and 2.1 kb are involved in their production, the synthesis of which is under the control of two respective promoters, namely S1 and S2. L-HBsAg is translated from the 2.4 kb transcript, while the M- and S-HBsAgs are translated from the 2.1 kb transcript, the latter through leaky ribosome scanning.

The fourth and smallest ORF encodes for the 17kD HBx protein which is translated from the shortest 0.7 kb in length transcript. This protein is necessary for viral replication and has been implicated in several cellular functions such as cell cycle regulation, signal transduction, transcriptional activation, and DNA repair [5].

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