Virus Research 213 (2016) 205–213

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Review

Recent developments in antivirals against hepatitis B virus

Ya-Juan Wang., Li Yang*, Jian-Ping Zuo*

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Zuchongzhi Road 555, Shanghai, People's Republic of China

ARTICLE INFO

Article history:
Received 13 November 2015
Received in revised form
21 December 2015
Accepted 21 December 2015
Available online 28 December 2015

Keywords:
Hepatitis B
Antiviral therapy
Inhibitory drugs
Host immune regulators

ABSTRACT

Chronic hepatitis B virus (HBV) infection (CHB) is a major cause of cirrhosis and hepatocellular carcinoma (HCC). Although the availability of HBV vaccines effectively reduces the incidence of HBV infection, the healthcare burden from CHB remains high. Several antiviral agents, such as (pegylated-) interferon-α and nucleos(t)ide analogs are approved by US FDA for chronic HBV infection management. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been recommended as the first-line anti-HBV drugs for excellent viral suppression with a low risk of antiviral resistance, but the cost and need for essentially life-long treatment are considerable challenges. And none of these current treatments can eradicate the intracellular virus. Given these issues, there is still an unmet medical need for an efficient HBV cure. We summarize here the key developments of antivirals against hepatitis B virus, including HBV replication cycle inhibitors and host immune regulators.

Contents

1. HBV prevalence

Worldwide there are more than 248 million chronic hepatitis B virus (HBV) carriers (Mortality and Causes of Death, 2015). According to the global burden of Disease (GBD) study in 2013, hepatitis B infection led to 300,000 deaths globally (Global Burden of Disease Cancer et al., 2013). The clinical outcome of HBV infection is strongly influenced by the age of infection. Over 90% of newborns from HBeAg-positive mothers while less than 10% of adults with acute HBV progress to chronic infection (Locarnini et al., 2015).

Since 1981, a safe and effective vaccine against HBV infection, most of which in use are made from recombinant DNA that express HBsAg only, has been available to induce immunity in unexposed people (Trepo et al., 2014). The vaccine led to a significant decrease in the incidence of HBV infection. In Taiwan, the proportion of child HBsAg carriers decreased from 10% in 1984 (Chen, 2009), to 0·9% in 2009 (Ni et al., 2012). In the US, during the period 1999–2006, the prevalence of HBV infection decreased in people aged 6–19 years (from 1.9–0.6%; $P < 0.01$) and 20–49 years of age (5.9–4.6%; $P < 0.01$) (Sundaram and Kowdley, 2015; Wasley et al., 2010), and the age-adjusted prevalence of HBsAg (0.27%) in 2013 (Schweitzer et al., 2015) was not statistically different from what they were in 2006 (Wasley et al., 2010).

* Corresponding author.
E-mail addresses: yangli@simm.ac.cn (L. Yang), jpzuo@simm.ac.cn (J.-P. Zuo).

http://dx.doi.org/10.1016/j.virusres.2015.12.014
0168-1702/

2. HBV molecular biology and replication cycle

HBV, a member of Hepadnaviridae family, is a DNA virus with an envelope surrounding an icosahedral capsid. The capsid contains HBV genome DNA and the viral polymerase (Pol). HBV genome comprises a relaxed-circular, partially double-stranded 3.2 kb DNA (rcDNA), which contains four open-reading frames and encodes the surface protein, the core protein/the hepatitis B e antigen (HBeAg), the viral polymerase and the viral X protein (Liang, 2009).

HBV virion enters the hepatocytes by binding with the sodium-taurocholate cotransporting polypeptide (NTCP) receptor (step A) and is uncoated (step B). The naked nucleocapsid is transported to the nucleus, and the HBV genome is integrated into the host genome (step C), or converted into a covalently closed circular DNA (cccDNA), which serves as the transcriptional template (step D). After HBV RNAs transcription (step E) and HBV proteins synthesis (step F), the nucleocapsid is formed in the cytosol, and during this process a pregenomic RNA (pgRNA) and viral polymerase (Pol) are incorporated into the assembling core (step G). Once pgRNA is encapsidated, reverse transcription begins and (−) DNA strand is synthesized from the pgRNA template by reverse transcriptase activity of Pol (step H), followed by pgRNA degradation by RNase H activity of Pol and synthesis of the (+) DNA strand by the DNA polymerase activity of Pol (step I). Mature nucleocapsid is then either directed to the secretory pathway for envelopment with L, M, and S surface proteins (step J), or recycled into the nucleus to amplify the cccDNA pool (step K). The envelope protein can be secreted as small, non-infectious subviral particles, and the precore protein is secreted as HBeAg (step L) (Fig. 1).

The complex steps of HBV replication cycle, including hepatocyte entry, replication, nucleocapsid formation, and release, are all potential targets for antivirals. And given the importance of host immune regulation in HBV cure, agents targeting innate or adaptive immunity are currently undergoing development for viral control (Baumert et al., 2015).

3. Current available therapies of hepatitis B

Several antiviral agents are approved by the United States Food and drug administration (FDA) for the management of chronic HBV infection (CHB): interferon-α (IFN-α) and (pegylated-) IFN-α, and five nucleos(t) ide analogues (NAs), including lamivudine (LMV), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF) (Fig. 2) (Trepo et al., 2014). (Pegylated-) IFN-α has a weaker antiviral activity than NAs, but is associated with a higher rate of HBeAg and HBsAg loss. The NAs can efficiently inhibit HBV replication by targeting the viral reverse transcriptase. Although the resistance problem to the NAs has been solved by TDF and to a lesser extent by ETV, all the NAs have no direct effect on viral transcription, translation or cccDNA, which means that the NAs are highly effective at suppressing viral replication, but rarely lead to the loss of HBsAg and the eradication of the intracellular virus (Boettler et al., 2014; Gish et al., 2015). It was reported that CHB patients who have achieved a serologic resolution of infection (loss of HBsAg, undetectable serum HBV DNA, appearance of anti-HBs) can experience reactivation of their disease as a consequence of immunosuppression or the use of anti-inflammatory medications (Perrillo et al., 2015; Reddy et al., 2015; Seetharam et al., 2014). Therefore, the development of new classes of HBV inhibitors and therapeutic strategies, including combination therapies, will be needed to ultimately cure the majority of CHB patients (Zeisel et al., 2015). In this review, we attempt to summarize the current advances in the field of antivirals against HBV and their targets, including HBV replication cycle inhibitors and host immune regulators (Table 1).

4. Emerging antivirals

4.1. HBV replication cycle inhibitors

4.1.1. HBV entry inhibitors

Maintenance of chronic HBV infection is thought to depend on a dynamic turnover of infected hepatocytes that are cleared by the immune system and cells that become newly infected. Previous studies suggested that hepatocyte turnover is much faster in HBV-infected liver than in healthy hepatocytes. HBV entry inhibitors may contribute to the eventual clearance of the virus with prolonged therapy by reducing newly infected hepatocyte (Volz et al., 2013).

HBV entry is essential for the initiation, spread, and maintenance of viral infection. The process involves the interaction between viral envelope proteins and cellular receptors. The establishment of HepaRG cell line (Gripon et al., 2002) and systems based on primary human hepatocytes and primary Tupaia belangeri hepatocytes have facilitated investigations of the cellular and viral determinants involved in HBV entry (Wang and Chen, 2014). It has been well documented that the N-terminus (amino acids 1–47) of HBV preS1 domain of the large viral envelope protein (L protein) is an essential element for viral entry (Schieck et al., 2013). The evidence suggests that Myrcludex-B, a synthetic myristoylated lipopeptide of this region, sequence-specifically and acylation-dependently targets hepatocytes and efficiently blocks de novo HBV infection both in vitro (Barrera et al., 2005; Glebe et al., 2005; Schulze et al., 2010) and in vivo (Petersen et al., 2008). Moreover, because upon viral entry, HBV genome is released into the cell nucleus, then the rcDNA is converted into the cccDNA, Myrcludex-B can efficiently hinder the amplification of the cccDNA pool in initially infected hepatocytes. Therefore, Myrcludex-B both sheds light on the molecular mechanism of HBV entry into hepatocytes and provides a basis for the development of potent hepadnaviral entry inhibitors as a novel therapeutic concept for the treatment of hepatitis B (Volz et al., 2013). Currently Myrcludex-B is being evaluated in phase II clinical trials (Haefeli et al., 2012).

Heparan sulfate proteoglycan (HSPG) is believed to be involved in the initial binding process of HBV entry (Leistner et al., 2008; Schulze et al., 2007), but a more specific and high-affinity cellular receptor on hepatocytes should be involved in HBV strict tissue specificity. Recently, through a combined approach of using biochemical and proteomic analyses with primary cultures of treeshrew hepatocytes, sodium/bile acid cotransporter (SLC10A1, also known as human sodium taurocholate cotransporting polypeptide or NTCP) was discovered to be involved in HBV (mainly the pre-S1 domain) and host interaction (Ezzikouri et al., 2014; Ni et al., 2014; Yan et al., 2015a). The identification of NTCP as a functional receptor for HBV may lead to novel inhibitors against the viral infection in the future (Yan et al., 2015a; Yuen and Lai, 2015). Chemicals that inhibit hNTCP metabolic functions have been tested for their efficiency in blocking HBV infection. For example, cyclosporine A (CsA) and its analogs can block HBV entry by cyclophilin-independent interference with the binding between NTCP and large envelope protein in vitro (Nkongolo et al., 2014; Watashi et al., 2014), and cyclosporine B shows the highest potency for inhibition of HBV infection among cyclosporine analogs (Iwamoto et al., 2014). Moreover, Irbesartan (Ko et al., 2015; Wang et al., 2015a), ezetimibe (Konig et al., 2014; Lucifora et al., 2013), and ritonavir, three FDA approved therapeutics with inhibitory potential on the metabolic function of hNTCP, can prevent infection at an early stage of the viral replication cycle (Blanchet et al., 2014). Another new inhibitor of HBV entry is a flavonoid present in green tea extract, epigallocatechin-3-gallate (EGCG), which can block the endocytosis/fusion step via clathrin-dependent endocy-