HHS Public Access

Author manuscript

Expert Rev Anti Infect Ther. Author manuscript; available in PMC 2015 May 19.

Published in final edited form as:

Expert Rev Anti Infect Ther. 2013 August ; 11(8): 755–757. doi:10.1586/14787210.2013.814846.

How further suppression of virus replication could improve current HBV treatment

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Keywords

curative therapy; drug development; hepatitis B virus

HBV: Its medical impact & the current state of therapy

Hepatitis B virus (HBV) is a small DNA virus that replicates by reverse transcription in the liver [1]. It chronically infects >350 million people and causes liver failure and hepatocellular carcinoma, resulting in about 1 million deaths each year worldwide [2]. HBV infections are primarily treated with nucleos(t)ide analogs (lamivudine, adefovir, entecavir, telbivudine and tenofovir) that block viral DNA synthesis, although pegylated IFN-α is used in some cases [3]. Long-term nucleos(t)ide analog therapy suppresses viral replication by 4–5 $\log_{10}$ in the majority (70–90%) of patients, often to below the typical clinical detection limit of 160–200 copies/ml. However, nucleos(t)ide analog therapy clears the infection as measured by loss of the HBV surface antigens (HBsAg) in serum in only 3–6% of patients even after years of treatment [4–6]. Drug resistance to the nucleos(t)ide analogs was a large problem with the earlier nucleos(t)ide analogs, but resistance to the newer drugs entecavir and tenofovir is very low or absent [7]. Nucleos(t)ide analog therapy has hence converted the pathology associated with HBV infections from a steadily worsening disease into a controllable condition for a majority of patients [8]. However, this control entails indefinite

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Financial & competing interests disclosure: The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

No writing assistance was utilized in the production of this manuscript.

administration of the drugs and expenses of about US$400–600 per month [9]. Furthermore, there is a potential for unpredictable side effects that may be induced by decades-long exposure to the drugs. Despite these limits to the clinical efficacy of the nucleos(t)ide analogs, their ability to profoundly suppress HBV viremia in most patients and eliminate HBsAg in a minority of patients has shifted the goal of drug development from containment of HBV to a clinical cure.

The HBV genomic replication cycle & the definition of a 'cure'

The HBV replication cycle in chronically infected cells begins with production of a pregenomic RNA transcript from the nuclear episomal form of the viral genome, the covalently closed circular DNA (cccDNA). The pregenomic RNA is the template for reverse transcription, which occurs in the cytoplasm within nascent capsid particles. Newly synthesized genomes in these capsids can either be enveloped and secreted from the cell as mature virions, or they can be transported into the nucleus to replenish the nuclear cccDNA pool in a process called 'recycling' [1]. Thus, the cccDNA is the key genomic form of HBV during chronic infection.

It is becoming evident that the cccDNA is not completely eradicated from the liver even following resolution of an acute infection, but appears to be held in check at extremely low levels by host processes, presumably immune mechanisms [10]. This residual infection becomes clinically relevant only in some cases of immuno-suppression. Therefore, the definition of a 'cure' for an HBV infection is being reconsidered [11], but we regard a clinical cure to be equivalent to the stable near-eradication of the cccDNA that is achieved by natural resolution of an acute infection.

Why nucleos(t)ide analog therapy does not usually cure HBV

Transfer of newly synthesized viral genomes into the nucleus via recycling is tightly regulated because cccDNA levels stay constant at approximately ten to 50 copies per cell even as viremia can vary over many orders of magnitude. This implies that recycling would be favored at very low viral replication levels, and hence that it would be possible to suppress HBV replication far enough to eliminate secretion of virions while still permitting ongoing replenishment of the cccDNA through low levels of residual viral replication. This, in effect, is what current antiviral therapy targeting the reverse transcriptase achieves: reduction of secreted mature viral particle below detectable limits in the serum but failure to interrupt maintenance of the cccDNA pool. Residual HBV replication during apparently effective nucleos(t)ide analog therapy is confirmed by the sequential accumulation of resistance mutations during therapy [7,12] which cannot occur without ongoing cccDNA synthesis.

Suppressing HBV synthesis below the threshold needed to maintain the cccDNA by further improving the nucleos(t)ide analogs is unlikely. This is because these drugs are all similar prodrugs whose failure to suppress HBV far enough to clear the infection is due to competition with natural dNTPs for the viral DNA polymerase active site, limited phosphorylation to their active triphosphate forms and restrictions to their intracellular concentrations that are determined by their stability and import– efflux rates. It is also

possible that the active forms of these drugs accumulate to lower levels in subsets of cells in the liver, but we are unaware of data directly supporting this possibility. Furthermore, combinations of multiple nucleos(t)ide analogs do not work better than monotherapy in most cases [7], eliminating another avenue for improved therapy employing just nucleos(t)ide analogs. Together, these issues indicate that HBV clearance will require novel drugs that act on targets other than the DNA polymerase active site and that are under a different set of pharmacological constraints than the nucleos(t)ide analogs.

Therapeutic approaches that could lead to a cure for HBV

HBV could theoretically be eliminated from the liver by increasing the decay rate of the cccDNA and/or by blocking its synthesis long enough to permit natural turnover to remove the cccDNA.

The cccDNA turnover could be accelerated with novel immune-mediated therapies that promote restoration of HBV-specific immunity. This should be feasible because the immune system can non-cytolytically destroy most of the cccDNAs in the liver without severely affecting liver function during resolution of acute HBV infection [13]. Achieving this response therapeutically has been challenging because immunity to the virus is functionally exhausted in chronically infected patients. Novel therapeutic vaccines using new vectors for antigen delivery [14,15] and experimental strategies such as gene therapy to reconstitute virus-specific T-cell immunity [16,17] are showing potential in restoring virus-specific immunity. However, care will need to be taken during development of immunotherapies due to their potential to induce flares of hepatitis, especially given the heterogeneity of the human population and HBV's complex clinical presentation.

Clearing HBV by suppressing cccDNA synthesis could also be achieved with new drugs that block HBV's genomic replication cycle well enough to allow the cccDNA to decay naturally. Examples of novel inhibitors that are under investigation include compounds that directly block cccDNA formation [18] and inhibitors of the HBV RNAse H activity [19]. New direct-acting anti-virals will need to have minimal toxicity because many potential recipients will have advanced liver disease that can heighten drug sensitivity.

Prospects for achieving a clinical cure for HBV infections by attacking genomic synthesis will be dependent upon the half-life of the cccDNA in the liver. This is because cccDNA loss would be due to turnover of the cccDNA within cells and death of infected hepatocytes. Estimates of cccDNA half-life vary from a few days to infinity, so it is unclear how long viral replication would have to be profoundly suppressed. The precedent of successfully clearing HBsAg with nucleos(t)ide analog therapy in a few percent of patients implies that the cccDNA's effective half-life is finite but long. This in turn implies that the clearance or stable suppression of HBV will require a long treatment period with direct-acting inhibitors, probably a year or longer.

Pharmacologically curing a large proportion of HBV patients is almost certain to require multiple drugs. These combinations will quite possibly include both immunomodulatory and direct-acting drugs that simultaneously increase the decay rate of the cccDNA in the liver and block its replenishment. The agents in these combinations will need to complement each

other with regard to efficacy, mode of action and pharmacological parameters. The existing nucleos(t)ide analog drugs are very likely to be included in these drug cocktails due to their high efficacy and low toxicity.

Benefits of enhancing pharmaceutical suppression of HBV replication

We see four possible benefits from improving the control of HBV replication. First, combining new drugs that act additively or synergistically with the nucleos(t)ide analogs would improve control of the virus in the minority of patients for whom nucleos(t)ide monotherapy is inadequate to suppress viral titers below the clinical detection limit. Second, adding another drug that suppresses HBV by inhibiting a target other than the DNA polymerase active site would increase the genetic barrier to evolution of drug resistance and would lengthen the time that inexpensive drugs such as lamivudine retain effectiveness. This could have a major impact on HBV's disease burden in resource-limited settings where lamivudine is still widely used despite its resistance profile because it is the only drug many patients can afford. Third, HBV's proteins, including HBeAg, HBsAg and the reverse transcriptase, have immunosuppressive activities and are believed to contribute to the immunological defects that prevent clearance of the virus during chronic infection. Suppressing viral replication far enough to suppress covalently closed circular DNA levels would reduce production of the viral proteins and lessen their immunosuppressive potential, and this could lead to improved immune responses that would assist in controlling HBV. Long-term antiviral therapy has already been shown to partially restore HBV-specific immunity [20]. Finally, if viral replication can be suppressed far enough for long enough, even direct-acting drugs by themselves could achieve a clinical cure in many more patients than is feasible today.

Acknowledgments

J Tavis has received funding from the NIH for his work on the HBV polymerase (R01 AI38447, R 21 CA91327 and R43 AI84232) and from the Friends of the Saint Louis University Liver Center. He has received consultancy fees from Roche Diagnostics, Inc. and Alios BioPharma relative to anti-HBV therapy. Y Hu has received a National Sciences Foundation of China award (NSFC 81101310) and the Research Fund for the Doctoral Program of Higher Education of China award (20115503120001) related to the HBV polymerase. A Gehring has received Research Licensing fees from Hoffman La Roche related to T cell receptor gene therapy. Tavis and Hu are inventors on provisional US patent application 61/730,344 (pending) relevant to anti-HBV RNAseH inhibitors.

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