OPEN ACCESS Freely available online

Journal of Antivirals & Antiretrovirals

Editorial

Combination Therapy: A Key to The Elimination of HBV cccDNA

Kabo Baruti*

Department of Biological Sciences, University of Botswana, Gaborone, Botswana

DESCRIPTION

Hepatitis B Virus (HBV) poses a significant global health problem, with approximately 257 million individuals chronically infected worldwide, causing 887 000 deaths per annum [1]. Healthy individuals are able to resolve infection within the first six months of infection (acute stage). However, infection may persist for longer than 6 months resulting in Chronic Hepatitis B infection (CHB), which is characterized by the presence of the Hepatitis B virus surface Antigen (HBsAg) [1]. Furthermore, CHB results in complications such as cirrhosis, endstage liver disease and hepatocellular carcinoma, which are the causes of high mortality rates [1].

HBV infects host liver cells (hepatocytes), by attaching to the Sodium Taurocholate Cotransporting Polypeptide (NTCP) receptor, and then releases its nucleocapsid which contains Deoxyribo Nucleic Acid (DNA) into the cytoplasm [2]. The nucleocapsid is then transported to the nucleus where the viral DNA is converted from its relaxed circular form to closed covalent circular DNA (cccDNA) [2]. The cccDNA is transcribed into HBV pregenomic Ribo Nucleic Acid (pgRNA) and several subgenomic RNAs [2].

There are three categories of HBV cure which are: virological, functional (immunological), and partial cure [3]. Virological cure is defined as eradication of HBV DNA from the blood and liver with continued positive serological test results for Hepatitis B core antibodies (anti-HBc) with or without Hepatitis B surface antibodies (anti-HBs) [3].

Functional cure is defined as HBsAg loss combined with undetectable levels of HBV DNA in the peripheral blood that is sustained indefinitely after a finite course of therapy [3]. Partial cure is characterized by a low (<2000 IU/mL) to undetectable level of HBV DNA maintained indefinitely after treatment is stopped, but with detectable HBsAg [3].

HBV can be treated with drugs such as pegylated interferon α [4], which have been shown to induce a long-term and sustainable suppression of cccDNA transcription in-vitro, possibly by altering epigenetic modification of cccDNA minichromosomes [5]. However, the effect of pegylated interferon α on human subjects is yet to be determined in clinical trials. Nucleos(t)ide Analogues (NAs) such as lamivudine, entecavir, telbivudine, adefovir dipivoxil and tenofovir which are primarily used as antiretrovirals for the treatment and management of Human Immunodeficiency Virus (HIV) have also been reported to have anti-HBV activity [6]. Their mode of action is that they inhibit HBV replication by targeting the viral RNA-dependent DNA polymerase which catalyzes the reverse transcription of pre-genomic RNA (pgRNA) to mature viral DNA [6]. The aim of these drugs is to achieve functional cure as aforementioned.

However, these drugs cannot completely remove HBV DNA from the body, due to the persistence of cccDNA which acts as a reservoir for viral reactivation [6]. Significant progress has been made in the understanding of the cccDNA biology such as the identification of novel host dependency factors and previously unknown mechanisms of epigenetic regulation of cccDNA transcription [6]. Therefore, the best therapeutic strategy for the complete elimination of HBV involves reduction or elimination of the whole cccDNA. Novel therapeutic strategies which affect cccDNA in a direct or indirect manner include genome editing, epigenetics and gene regulation, host-targeting approaches, nucleocapsid assembly and immunity [6].

The gene editing systems that have been reported to disrupt cccDNA include the Zinc Finger Nuclease (ZFN), Transcription Activator-Like Effector Nucleases (TALENs) and the Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated (CRISPR/Cas) system [6]. These systems work by creating a DNA double-strand break in a specific target site and repair the cleavage sites by altering DNA sequence[6]. The CRISPR/Cas9 system was the most successful, showing anti-HBV activity demonstrated by suppression and reduction of intrahepatic cccDNA in vivo, consistent with the cell culture results [7].

However, challenges of these gene editing systems such as off-target effects and delivery still remain. Overcoming these challenges, which should now be the main focus as far as HBV is concerned, requires detailed understanding of these mechanisms in patients. Furthermore, finding the synergistic effect of these molecular biology-based techniques with NAs may be the solution to eliminating cccDNA and finding the cure for HBV. Achieving this will represent a step in the right direction and is in line with achieving sustainable development goals of 2030 which aims to reduce new viral hepatitis infections by 90% and reduce deaths due to viral hepatitis by 65% by the year 2030.

Corresponding to: Kabo Baruti, Department of Biological Sciences, University of Botswana, Gaborone, Botswana, E-mail: kabobaruti@gmail.com

Received date: December 7, 2020; **Accepted date:** December 22, 2020; **Published date:** December 29, 2020

Citation: Baruti K (2020) Combination Therapy: A Key to The Elimination of HBV cccDNA. J Antivir Antiretrovir. S10: e002

REFERENCES

1. World Health Organization. Hepatitis B Fact Sheet n.d. (2020).
2. Zhu A, Liao X, Li S, Zhao H, Chen L, Xu M, et al. HBV cccDNA and its potential as a therapeutic target. J Clin Transl Hepatol. (2019);7(3):258.
3. Dareng EO, Adebamowo SN, Famooto A, Olawande O, Odutola MK, Olaniyan Y, et al. Prevalence and incidence of genital warts and cervical Human Papillomavirus infections in Nigerian women. BMC Infect Dis. 2019;19(1):27.
4. Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut. 2015;64(12):1972-1984.
5. Liu F, Campagna M, Qi Y, Zhao X, Guo F, Xu C, et al. Alpha-interferon suppresses hepadnavirus transcription by altering epigenetic modification of cccDNA minichromosomes. PLoS Pathog. 2013;9(9):e1003613.
6. Ligat G, Goto K, Verrier E, Baumert TF. Targeting Viral cccDNA for Cure of Chronic Hepatitis B. Curr Hepatol Rep. 2020;19(3):235-244.
7. Dong C, Qu L, Wang H, Wei L, Dong Y, Xiong S. Targeting hepatitis B virus cccDNA by CRISPR/Cas9 nuclease efficiently inhibits viral replication. Antiviral Res. 2015;118:110-117.