

Currently Available Anti-Hepatitis Viruses Drugs

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ABSTRACT

The hepatotropic hepatitis viruses (HAV, HBV, HCV, HDV and HEV) cause acute and chronic liver diseases, including cirrhosis and carcinoma in general population. While there are globally accessible vaccines for HAV and HBV, a recently approved HEV vaccine is restricted to China. Currently, there is a wide range of effective nucleoside analog-based antiviral drugs for treating chronic hepatitis B (e.g., Lamivudine, Adefovir, Tenofovir, Emtricitabine, Entecavir, Telbivudine, Famiciclovir and Ganciclovir) and hepatitis C (e.g., Ribavirin, Telaprevir, Simeprevir, Paritaprevir, Sofosbuvir, Daclatasvir, Elbasvir, Ombitasvir and Velpatsvir). However, Ribavirin is the only treatment option for chronic hepatitis E in immunocompromised patients. Nonetheless, viral mutants associated drug-resistance or

non-response to therapy remains a big challenge in clinical settings. Also, of the several popular herbal products used for hepatitis B and C, some are known to cause severe side-effects and hepatotoxicity.

Key words: Hepatitis viruses; HAV; HBV; HCV; HDV; HEV; Antiviral; Nucleoside analogs

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INTRODUCTION

Hepatitis viruses are inherently hepatotropic pathogens that cause acute and chronic liver diseases, including fulminant liver failure, cirrhosis and hepatocellular carcinoma^[1,2]. Since the discovery of hepatitis B virus (HBV) in 1965, followed by hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV), we have enormous information on their biology, mode of transmission and mechanisms of pathogenesis, including preventive and therapeutic measures^[2,3]. Despite globally available vaccines for HAV and HBV, and effective antiviral drugs against HBV, HCV, HDV and HEV, millions of deaths occur of chronic hepatitis annually. Recently, an approved HEV vaccine is marketed in China that however, still waits global access^[4]. In addition, new hepatotropic viruses such as hepatitis F virus (HFV), hepatitis G virus (HGV), GB viruses (GBV), transfusion-transmitted virus (TTV) and SEN virus (SENV) have been also identified in chronic liver disease patients^[3]. Notably, all hepatitis viruses have RNA genome except HBV that uniquely replicates its DNA via a pregenomic RNA intermediate and therefore, also called pararetrovirus.

ANTIVIRAL DRUGS

Antiviral drugs are diverse and wide spectrum chemotherapeutic agents, classified according to their target viruses, chemical structures and modes of action^[5]. Of these, the nucleoside analogs (NAs) are viral polymerase/reverse-transcriptase (Pol/RT) inhibitors that terminate the growing nascent DNA/RNA chain. Historically, in the last two decades, important antivirals have been developed against

the retroviruses, such as human immunodeficiency virus (HIV), herpes simplex virus (HSV) and cytomegalovirus (CMV) infections^[6]. The anti-HIV NAs are generally direct-acting (DAA) RT-inhibitors, such as Zidovudine, Lamivudine, Adefovir, Entecavir, Tenofovir, Emtricitabine, Abacavir, Stavudine and Didanosine. The non-NA RT-inhibitors include Delavirdine, Efavirenz, Etravirine, Nevirapine and Rilpivirine etc. The anti-HSV NAs are Acyclovir, Valacyclovir, Cidofovir, Famciclovir, Ganciclovir and Valganciclovir^[5]. Some other NAs, like Fialuridine, Didanosine and Zalcitabine, including Stavudine can however, cause direct (mitochondrial dysfunction) or indirect (idiosyncratic) hepatotoxicity as well as exacerbation of underlying liver disease^[7,8]. Interestingly, majority of the anti-retroviral drugs are also found to act against genetically close hepatitis viruses.

ANTI-HBV DRUGS

HBV causes acute and chronic hepatitis B in about one-third of world's population, of which approximately 360 million are at risk for developing liver cirrhosis or carcinoma^[9]. Because of genetic similarity, several anti-HIV (e.g. Lamivudine, Adefovir, Tenofovir, Emtricitabine, Entecavir and Telbivudine) and anti-HSV (e.g., Famciclovir and Ganciclovir) NAs are also effective in treating chronic hepatitis B. Basically, almost all approved anti-HBV drugs were first developed against HIV or HSV. Though these drugs are very effective, generally safe and well tolerated, prolonged treatment with Lamivudine, Adefovir, Famciclovir or Entecavir often leads to drug-resistance due to emergence of viral Pol/RT mutants^[10]. In addition, chemokines like interferon alpha (pegIFN- α -2a) is also active but are no longer commonly used because of non-response or side-effects in some chronic patients. In addition, there are several herbal formulations or natural products popular as traditional Chinese medicine (TCM), such as Zexie, Bo He, Chuan Lian Zi, Gan Cao, Ji Guo Cao, Jue Ming Zi, Long Dan Xie Gan Tang, Chai Hu, Bai Fang and Zhen Chu Cao etc. used for hepatitis B^[11,12]. Nonetheless, some of them are reported to cause hepatotoxicity and other serious side-effects^[13].

ANTI-HCV DRUGS

HCV infects over 180 million people worldwide, of which about 70 million chronic cases remain at high risk of developing liver cirrhosis and carcinoma^[14]. The anti-HCV drugs include the NA drug Ribavirin and pegIFN- α -2a, generally given in combination for sustained virological response (SVR). In addition, the HCV RT-inhibitors (ending with -asvir or -buvir; e.g., Daclatasvir, Elbasvir, Lepidiasvir, Ombitasvir, Velpatasvir, Sofosbuvir, Dasabuvir and Pibrentasvor) and protease-inhibitors (ending with -previr; e.g., Boceprevir, Telaprevir, Simeprevir, Paritaprevir, Grazoprevir and Glecaprevir) are currently available^[5, 15]. Combinations of two or more of these drugs (Harvoni, Technive, Viekira Pak, Zepatier, Epclusa and Mavyret) with enhanced activity are also marketed. Nonetheless, non-response or failure of some DAA therapy is also observed due to emergence of HCV mutants in a proportion of chronic patients^[16]. Further, TCM like Silymarin when consumed with DAA like, Simeprevir is related to hepatotoxicity in some HCV patients^[13,17]. Another widely used anti-HCV natural product Glycyrrhizin is also known to affect drug-metabolizing enzymes and efflux transporters^[18].

ANTI-HDV DRUGS

HDV is a satellite virus of HBV, which is estimated to co-infect about 13% of chronic hepatitis B patients (60 million), worldwide^[19]. It is the most severe form of viral hepatitis with the highest risk to devel-

oping liver cirrhosis and carcinoma. To date, only pegIFN- α -2a is recommended for HDV infection where poor response rates, intolerance or ineligibility in many patients remains a big challenge^[20].

ANTI-HEV DRUGS

HEV is a genotype-specific water-/foodborne or zoonotic virus that causes acute and chronic hepatitis E with a fatality rate of ~2%, including 20-30% of pregnant women^[21,22]. Needless so far, there has been no treatment for self-limiting acute hepatitis E. However, with the emergence of chronic infections, especially in patients who have received solid-organ transplants or cancer chemotherapy, Ribavirin and pegIFN- α -2a are the only anti-HEV regimens^[23,24]. Though Ribavirin effectively inhibits HEV replication and induce SVR, drug-resistance associated mutations in HEV RNA-dependent RNA polymerase (RdRP) lead to non-response or therapeutic failure in immunocompromised patients^[25,26]. Very recently in a couple of case studies, Sofosbuvir co-treatment with Ribavirin has shown improved viral clearance^[27,28].

CONCLUSION

Despite scientific advancement in virus pathobiology and therapeutics, chronic hepatitis B, C and E remain globally important health issues. A wide range of effective NA-based drugs is currently available for treating viral hepatitis. However, viral mutants associated drug-resistance or non-response to therapy remains a big challenge in clinical settings. In addition, some popular herbal anti-hepatitis B and C products are also related to severe side-effects and hepatotoxicity. Therefore, non-NA agents as well as promising bioactive natural products with no side-effects or drug-resistance in clinical trials offer future anti-hepatitis drugs.

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