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EDITORIAL

Management of hepatitis delta: Need for novel therapeutic options

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Abstract

Hepatitis D virus (HDV) is the smallest single stranded RNA virus infecting humans. The hepatitis B surface antigen envelope protein protects the HDV nucleocapsid antigen and provides a means for the virus to enter and exit the hepatocyte. Hepatitis B and D viruses exploit the human sodium taurocholate co-transporting polypeptide (NTCP), a receptor, for their entry into hepatocytes. Prenylation of the large delta antigen is a critical determinant of HDV particle assembly. Treatment with pegylated interferon results in sustained virological response six months post-treatment in one fourth of the patients. Nucleos(t)ide analogs (NAs) have been widely tested in hepatitis delta, but they appear to be ineffective. Combination treatment of NAs with interferon also proved to be disappointing so there is a need for novel therapeutic options. The receptor function of NTCP is blocked by Myrcludex B, a synthetic N-acylated preS1 lipopeptide that competes with infectious virions for receptor binding. There are already some approved drugs available, including irbesartan, ezetimibe, and ritonavir and cyclosporin A, with documented inhibitory effects on NTCP's metabolic function. These drugs may have a role in HDV treatment. Interference with host-mediated post-translational changes of proteins that are crucial to the HDV life cycle, such as prenylation may become an important tool to control HDV infection and prevent replication. Lonafarnib, a prenylation inhibitor significantly reduces virus levels in hepatitis delta patients. Antisense oligodeoxynucleotides which are complementary to genomic HDV ribozyme self-cleavage site and stem I regions can inhibit genomic HDV ribozyme activity.

Key words: Hepatitis D virus; Hepatitis delta; Interferon; Lonafarnib; Prenylation inhibitors; Myrcludex

Core tip: The human sodium taurocholate cotransporting polypeptide (NTCP) has been identified as a functional, preS1-specific receptor for hepatitis B and D virus entry. New antiviral drugs will target this receptor to control hepatitis delta infection. There are

already a few approved drugs available in the market with inhibitory effects on NTCP. Interference with host-mediated post-translational changes of proteins that are crucial to the Hepatitis D virus (HDV) life cycle, such as prenylation may become an important tool to prevent HDV replication. These developments are important since pegylated interferon maintains a sustained virological response in just a quarter of all patients.

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INTRODUCTION

Hepatitis D virus (HDV) is the smallest single stranded RNA virus infecting humans. It is a defective virus that requires hepatitis B surface antigen (HBsAg) for transmission. The virus particle has a circular genomic RNA, encoding small and large delta antigens (S-HDAg and L-HDAg) and a surrounding lipid envelope embedded with HBsAg. S-HDAg is required for the initiation of viral genome replication, whereas L-HDAg serves as a principal inhibitor of replication and is essential for the assembly of new virion particles[1,2]. The HBsAg envelope protein protects the HDV nucleocapsid antigen and provides a means for the virus to enter and exit the hepatocyte. Hepatitis B and D viruses exploit human sodium taurocholate co-transporting polypeptide (NTCP) for species-specific entry into hepatocytes[3]. HBsAg is not necessary for the replication of HDV once it has entered the cell.

Worldwide, there are approximately 240 million individuals chronically infected with the hepatitis B virus (HBV), including 15-20 million coinfected with the hepatitis D virus[4]. The disease continues to be a major medical scourge in the Asia Pacific region, specially Pakistan, Mongolia and Eastern Europe[5]. Hepatitis delta (D) occurs either as coinfection with acute hepatitis B or as a superinfection in patients with pre-existing chronic HBV infection. Chronic hepatitis D is a serious form of chronic liver disease with an accelerated course leading to early cirrhosis, decompensation, and hepatocellular carcinoma[6].

INTERFERON BASED THERAPIES

No specific therapy exists for hepatitis D. Interferon (IFN) alpha, standard or pegylated, is the only approved option available so far. The rate of response is proportional to the dose of IFN, with 9 million units (MU) three times a week being more effective than 3 MU thrice weekly[7]. Conventional interferon given for one year results in end-of-treatment virological and biochemical response in one third of the patients. However, sustained virological response (SVR) at 6 mo post treatment is only seen in 17% of patients[8]. Treatment with pegylated interferon (PEG-IFN) results in SVR six months post-treatment in one fourth of the patients[6,9]. Weekly injection of PEG-IFN is currently used for 12 to 18 mo. SVR at six months correlates with absence of advanced fibrosis in most cases[10]. Late HDV RNA relapses may occur after PEG-IFN therapy of hepatitis delta and thus the term "sustained virological response" should be used with caution in HDV infection[11].

After initiation of therapy with PEG-IFN, a median delay of 9 d (interquartile range 5-15) was observed with no significant changes in HDV level. Thereafter, HDV declined in a biphasic manner, where a rapid first phase lasting for 25 d (inter quartile range: 23-58) was followed by a slower or a plateau second phase. None of the patients with flat second phase in HDV achieved complete virological clearance (CVR). The observation that a flat second phase in HDV and HBsAg kinetics was associated with failure to achieve CVR provides the basis to develop early stopping rules during PEG-IFN treatment in HDV-infected patients[12]. There is no impact of interferon lambda3 rs12979860 single nucleotide polymorphism on the long term drug induced hepatitis D clearance[13]. Response to the treatment can be predicted by the HDV RNA assessment at six months, which may give clues as to whether to stop treatment. Patients with negative HDV RNA at six months are more likely to have SVR[9] while non-responders could be identified by a less than 3 log decrease of HDV RNA at 6 mo of treatment[14]. Although no head to head comparison trials have been carried out using pegylated interferon alpha 2a or 2b, both therapeutic regimens appear to be equally effective.

Nucleos(t)ide analogs (NAs) have been widely tested in CDH, but they appear to be ineffective. Only one study has shown that Long-term exposure to tenofovir significantly reduced serum HDV-RNA apart from completely suppressing HBV-DNA in HIV-infected patients with hepatitis delta. This virological benefit was accompanied by significant improvements in liver fibrosis[15]. Combination treatment of NAs with IFNs does not provide any edge over PEG-IFN monotherapy in terms of suppressing HDV infection[16]. In the Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT 1) PEG-IFN with Adefovir arm given for 48 wk showed significant decline in HBsAg titers compared to PEG-IFN with placebo[17] but HIDIT 2 trial using the more powerful nucleotide analogue, tenofovir, in combination with pegylated interferon with increased treatment duration of up to 96 wk, failed to reproduce the earlier results of HBsAg decline[18].

VIRUS ENTRY INHIBITORS

Inhibition of virus entry has become a major concept

in the development of new antiviral drugs. Hepatitis B immunoglobulins have long been used to neutralize infection by binding to the S-domain of HBV surface proteins and preventing reinfection of the graft after liver transplantation. Recently, the human sodium taurocholate cotransporting polypeptide (NTCP) has been identified as a functional, preS1-specific receptor for HBV and HDV entry into hepatocytes[19]. It is therefore important to study the therapeutic potential of virus entry inhibitors, especially when combined with strategies to induce immune-mediated killing of infected hepatocytes. The large envelope (L) protein on the surface of HBV and HDV particles has many different functions and is required for virus entry. The HBV L protein mediates attachment of virions to heparan sulfate proteoglycans on the surface of hepatocytes. The myristoylated N-terminal preS1 domain of the L protein subsequently binds to the NTCP. The receptor functions of NTCP and virus entry are blocked by Myrcludex B, a synthetic N-acylated preS1 lipopeptide that competes with infectious virions for receptor binding[20]. Ni *et al*[3] identified 2 short-sequence motifs in human NTCP that were required for species-specific binding and HBV and HDV entry *via* NTCP.

A recent ongoing study has recruited 24 patients with hepatitis delta (compensated liver disease; 12.5% cirrhosis) scheduled for 48 wk of PEG-IFN therapy. Eight hepatitis delta patients are receiving pre-treatment with 2 mg Myrcludex B alone for 24 wk (B1); Myrcludex B was added to PEG-IFNa for the first 24 wk to another 8 patients (B2) while 8 patients are getting treatment with PEG-IFNa alone (B3). 6/7 and 7/7 of patients, whom data is available, experienced greater than one log reduction in HDV RNA levels at week 24 during Myrcludex B monotherapy or combination therapy while this response was observed in 7/7 of patients with PEG-IFNa monotherapy group at week 12. However, at week 24, HDV RNA became negative in two patients who received Myrcludex B alone and five patients who received its combination with PEG-IFNa. ALT values declined at week 24 in 6/7 (B1), 4/7 (B2) and 3/7 (B3, week 12) patients. One patient in B1 and one in B2 had both negative HDV RNA and normal ALT at week 24[21]. This is a small study, with only interim results available. However, it is apparent that at least end of treatment virological response will be better in the combination arm.

There are already some approved drugs available with documented inhibitory effect on NTCP metabolic function[22]. These FDA approved molecules include irbesartan, ezetimibe, and ritonavir. Irbesartan is an angiotensin Ⅱ receptor antagonist used primarily for the treatment of hypertension. Ezetimibe lowers plasma cholesterol levels, while ritonavir is an antiretroviral drug from the protease inhibitor class used to treat HIV infection. Blanchet *et al*[23] investigated the ability of these drugs to impair viral entry using a HDV *in vitro* infection model based on a NTCP-expressing Huh7 cell line. They demonstrated the potential of three FDA approved molecules to alter HDV infection *in vitro*. Another drug, cyclosporin A inhibits the binding of HBV preS to NTCP[24]. Nevertheless, its effect on HDV transmission needs further study. Administration of an entry inhibitor, possibly used in combination with current HBV drugs, may improve patients' treatment outcome.

PRENYLATION INHIBITORS

Interference with host-mediated post-translational changes of proteins that are crucial to the HDV life cycle, such as prenylation may become an important tool to control HDV infection and prevent replication. Molecular genetic studies have implicated the host-mediated post-translational changes of proteins such as prenylation of large delta antigen (LHDAg) as a critical determinant of HDV particle assembly. Moreover, it has been shown that the isoprenylation of L-HDAg induces liver fibrosis through the modulation of TGF-beta-induced signal transduction pathway[25]. Prenylation is the addition of hydrophobic molecules to a protein or chemical compound. Protein prenylation involves the transfer of either a farnesyl or a geranyl-geranyl moiety to C-terminal cysteine(s) of the target protein[26]. The enzymes that carry out prenylation in the cell are farnesyl transferase and geranylgeranyl transferase. Prenylation plays an important role in mediating protein-protein interactions and protein-membrane interactions.

Delta antigen prenylation can be pharmacologically inhibited by the prenylation inhibitor BZA-5B. BZA-5B is an inhibitor of farnesyltransferase activity. Furthermore, BZA-5B specifically abolishes particle production in a dose-dependent manner[27]. FTI-277, another farnesyltransferase inhibitor, prevented the production of complete infectious HDV versions of two different genotypes[28]. Farnesyltransferase inhibitors thus represent an attractive potential class of novel antiviral agents for use against HDV. In a recent phase 2a study in which 12 patients were treated with 100 mg twice daily (n = 6; termed group 1) or 200 mg twice daily for 28 d of lonafarnib, a farnesyltransferase inhibitor (termed group 2). After a delay of approximately 1 d in which HDV remained at baseline levels, a biphasic viral decline was observed. The 1st phase lasted for 7 to 21 d with greater (P = 0.04) viral decline from baseline in group 2 (median 0.95; inter quartile range: 0.69; log IU/mL) compared to group 1. So a dose dependent effect of lonafarnib in blocking HDV release was observed with efficacies of 67% and 87% in the 100 mg and 200 mg twice daily lonafarnib dosing groups, respectively[29,30]. Thus, the treatment of chronic HDV infection with the prenylation inhibitor lonafarnib significantly reduced the virus levels in these patients. This reduction in viral load in a short period of three weeks is interesting and merits further studies with longer duration of therapy. There is an unmet need to explore the efficacy and safety of combining a

viral entry inhibitor with the prenylation inhibitor in the next phase of the studies.

ANTISENSE OLIGONUCLEOTIDES

An antisense oligonucleotide is a short strand of deoxyribonucleotide analogue that hybridizes with the complementary mRNA in a sequence-specific manner *via* Watson-Crick base pairing[31]. Antisense therapy is a form of treatment for genetic disorders or infections. It is possible to synthesize a strand of nucleic acid that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it, effectively turning that gene "off". Alternatively, the strand might be targeted to bind a splicing site on pre-mRNA and modify the exon content of an mRNA. It has been shown that antisense oligodeoxynucleotides which are complementary to genomic HDV ribozyme self-cleavage site and stem I regions can inhibit genomic HDV ribozyme activity[32].

In conclusion, patients with hepatitis D should be treated with PEG-IFN for 12-18 mo. Long term monitoring is needed after the successful treatment to detect late relapses. Identification of NTCP as a functional, preS1-specific receptor for HBV and HDV is a great breakthrough and opens a new era of virus entry inhibitors. Delta antigen prenylation inhibitors are another group of drugs with potential to halt the spread of infection. It is therefore important to study the therapeutic potentials of these drugs, and evolve combined strategies to prevent viral entry, assembly, and transmission as well as induce immune-mediated killing of infected hepatocytes.

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