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HBV/HDV Coinfection: Emerging therapeutic options for a challenging disease.

Christopher Koh, MD MHSc,

Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Ben L. Da, MD,

Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Jeffrey S. Glenn, MD PhD

Departments of Medicine and Microbiology & Immunology, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Abstract

Chronic hepatitis D (CHD) results from an infection with hepatitis B virus (HBV) and hepatitis D virus (HDV). CHD is the most severe form of human viral hepatitis. Current treatment options consist of interferon alfa, which is effective only in a minority of patients. The study of HDV molecular virology has resulted in new approaches to therapy that have entered clinical trials, the most advanced of which has entered phase-3 studies. These include the entry inhibitor Bulevirtide, the nucleic acid polymer REP 2139-Ca, the farnesyltransferase inhibitor lonafarnib, and pegylated interferon lambda. This review summarizes available data of these emerging therapeutics.

Keywords

Hepatitis d; hepatitis b; clinical trials; therapeutics; cirrhosis

CORRESPONDING AUTHOR Christopher Koh, MD MHSc: Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Bldg. 10, Room 9B-16, MSC 1800, Bethesda, MD 20892 christopher.koh@nih.gov.

AUTHOR CONTACT INFORMATION

Christopher Koh, MD MHSc: Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, Bldg. 10, Room 9B-16, MSC 1800, Bethesda, MD 20892

Ben L. Da, MD: Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 10 Center Drive, CRC, Room 4-5722, Bethesda, MD 20892.

Jeffrey S. Glenn, MD PhD: Stanford University School of Medicine, CCSR Building, Rm. 3115A, 269 Campus Drive, Stanford, CA 94305

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Introduction

Hepatitis D (HDV) was first described by Mario Rizzetto and colleagues in 1977 and today is described as the most severe and rapidly progressive form of chronic viral hepatitis despite being an incomplete virus that requires the presence of hepatitis B virus (HBV) to be a human pathogen.[1, 2] Progression to cirrhosis occurs in 10-15% of patients within 2 years and in 70-80% within 5 to 10 years.[3, 4] Furthermore, HBV/HDV coinfection results in an increased risk of hepatocellular carcinoma (HCC)[5-11] and mortality[5, 7, 9, 12] compared to HBV mono-infection.

Although HDV infection has historically been thought of as a rare disease, recent estimations have suggested that the global burden of disease may be close to 62-72 million.[13] Despite these concerns, HDV does not currently have a US Food and Drug Administration (FDA) approved therapy. The only treatment that is used outside of clinical trials is pegylated interferon (peginterferon) but this treatment is plagued by significant side effects such as flu-like symptoms, myalgias, and arthralgias while having limited efficacy in HDV.[14] Nonetheless, it is currently the only treatment that is endorsed by the major liver societies such as the American Association for the Study of Liver Diseases (AASLD)[15] and European Association for the Study of the Liver (EASL)[16] due to its proven effect in reducing fibrosis, decreasing risk of hepatic decompensation, and improving mortality.[17-19] Numerous other treatments including HBV nucleoside analogs have been studied in clinical trials over the past several decades with and without interferon therapy without improvements in therapeutic response.[20-26] However, within the past decade, there has been a resurgence of interest in novel therapies in hopes of defeating this rapidly progressive and devastating disease.

In this review, we will highlight HDV virology and the viral life cycle, past therapeutic approaches, and current recommended therapies and their associated positive and negative aspects. Finally, we will discuss investigational therapies, their mechanisms of action, and the current progress and future of HDV therapeutics.

Virology and life cycle

The HDV virion is small RNA virus measuring ~ 36nm in diameter including an inner nucleocapsid that is made up of a short (~ 1.7 kb) single-stranded, circular RNA of negative polarity and ~ 200 molecules of hepatitis D antigen (HDAg).[27-29] This inner nucleocapsid is surrounded by a lipid envelope embedded with all three types of hepatitis B surface antigen (HBsAg) proteins obtained from HBV; without HBsAg, HDV is incapable of being a human pathogen.[30] The HDV genome is the smallest among mammalian viruses and shares structural similarity to viroids.[27, 28, 31] This genome encodes for one protein that exits in two forms; the small HDAg (SHDAg) and the large HDAg (LHDAg).

The HDV viral life cycle begins when the HDV virion binds to the human hepatocyte through interaction between the myristoylated N-terminus of the pre-S1 domain of the large HBsAg and the host receptor (Figure 1), also known as the sodium taurocholate cotransporting polypeptide (NTCP) located on the basolateral membrane of hepatocytes.

[32, 33] After cell entry and uncoating, the HDV genome is translocated to the nucleus via HDAg-mediated interactions where it employs host RNA polymerase II for genome replication. There are no DNA intermediates or archiving events.[34] Instead, HDV replication occurs via a double rolling circle mechanism driven by the catalytic activity of RNA polymerase II with the aid of SHDAg to create linear multimeric copies of antigenomic RNA from the incoming negative strand circular template genome.[35] These linear multimeric copies then undergo specific cleavage at a unique ribozyme site encoded once in each antigenome. The resulting linear antigenomic monomers are subsequently ligated into antigenomic circles that serve as template for production of linear multimers of opposite polarity genomic RNA. These in turn, self-process into linear genomic monomers via autocatalytic cleavage at another ribozyme site encoded once in each genomic RNA. The genomic monomers are ligated into circles which can either support additional rounds of replication or be packaged into nascent virions.[36]

A smaller antigenomic sense mRNA is also transcribed off of the genomic template. This mRNA codes for the two forms of HDAg.[35] The SHDAg and LHDAg are identical except that the LHDAg features an additional 19-amino acid sequence at the C-terminus resulting from a specific RNA editing event catalyzed by adenosine deaminase acting on RNA 1 (ADAR1) that effects the SHDAg stop codon.[37, 38] This results in translation proceeding to the next downstream stop codon and the addition of an extra 19 amino acids that characterize the LHDAg. This extra sequence on the LHDAg contains a CXXX-box motif (C=cysteine, X=one of the last 3 amino acids at the carboxyl terminus of the LHDAg) which then becomes the substrate for host cell farnesyltransferase. The latter covalently attaches a prenyl lipid farnesyl to the cysteine of the CXXX-box. This prenylation event is essential for virion assembly via promoting interaction with HBsAg.[39] In addition, the LHDAg is a potent transdominant inhibitor of genome replication while the SHDAg serves to promote genome replication.[40-42] Thus, the RNA editing event catalyzed by ADAR1 that changes the production of HDAg from SHDAg to LHDAg serves a key regulatory switch in the virus life cycle, shutting off genome replication and initiating virion assembly.

When the HDV virion is completed, it is ready for release via the trans-golgi network to infect new hepatocytes. After infection, hepatocyte damage caused by HDV infection can be due to a direct cytopathic effect of HDV or via still incompletely understood immune-mediated mechanism.[43-45]

HDV Therapeutics

Interferon-alpha therapy

Despite the lack of an FDA approved therapy for HDV infection, expert guidelines have recommended the use of peginterferon.[16, 46] These therapeutic recommendations stem from various experiences dating back to the early 1990s with the first use interferon alfa therapy. Initial experiences evaluated interferon alfa-2a at low doses (3 million IU TIW) compared with high doses (9 million IU TIW) or with no therapy for one year.[47] In this study, a complete response, defined as HDV RNA PCR negativity with ALT normalization, was seen in 21% of those treated with low dose interferon compared to 50% in those treated with high dose and 0% in those who did not receive any therapy. However, no patients demonstrated a

sustained virologic response in follow-up up to 48 weeks post-therapy. In this same cohort, a follow-up report of up to 14 years post-therapy with a more sensitive HDV RNA assay revealed that none of the original patients achieved HDV RNA negativity at the end of the original study. More importantly, long-term outcomes from this study demonstrated improved survival in the high dose group in those that achieved a ≥2 log drop in HDV RNA at the end of treatment (EOT) compared to those in the low dose group (p=0.019) and the no treatment group (p=0.003), both of which were unable to achieve a 2 log drop in HDV RNA at EOT.[18] Interestingly, there was no difference in survival between the low dose group and controls.

With the efficacy of peginterferon in other viral hepatitis infections, and the initial FDA approval of peginterferon alfa-2b in 2001 for chronic hepatitis C, it was then explored for use in chronic HDV infection. Peginterferon alfa-2b was administered (1.5 ug/kg/wk) for 1 year which resulted in undetectable HDV RNA in serum in 8 of 14 (57%) patients, however after a median post-therapy follow-up of 16 months, the sustained virologic response rate was 43%.[48] Prolonged peginterferon monotherapy has been studied for 72 weeks which resulted in low-level or undetectable HDV RNA in 34% of patients at the end of therapy, however with 24 weeks of post-therapy follow-up, only 21% of patients had undetectable HDV RNA.[21] Long-term peginterferon alfa-2a with increasing doses up to 360 mcg/wk has been studied for up to 5 years, however this has not resulted in improved response rates; only 30% of patients achieved a complete virologic response, described as HDV RNA negativity and HBsAg seroconversion.[49, 50] Thus, in chronic HDV infection, peginterferon appears to be as effective as standard interferon therapy and prolonged therapy does not appear to improve response rates. In fact, HDV RNA levels at 24 weeks of peginterferon therapy may predict response to one year of therapy.[51]

Interferon-alfa therapy combinations

Interferon alfa-based therapies have been studied in combination with other medications in chronic HDV infection. Interferon alfa, with and without pegylation, in combination with ribavirin has been studied in chronic HDV patients for 1 to 2 years, however, there does not appear be any added value of ribavirin in HDV.[20, 21, 52] Alternatively, HBV nucleoside analogues have also been evaluated, without much success, in combination with or without interferon alfa including famicyclovir[24], lamivudine[53], adefovir[26], and tenofovir.[54, 55] This is not surprising, since such HBV nucleoside analogs can be quite effective at decreasing serum HBV DNA but have no significant effect on HBsAg—which is all that HDV needs to replicate. One of the largest studies of peginterferon in HDV, the Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT-1) study, randomized 90 patients to adefovir, peginterferon, or the combination. An approximate 2.5 log decline in median HDV RNA was observed at 48 weeks of treatment in both peginterferon arms, with ~25% of these patients achieving HDV RNA negativity at 24 weeks post follow up. No responses were seen in the adefovir arm.[26] A follow-on study (HIDIT-2), which evaluated switching the nucleoside analog from adefovir to tenofovir and extending treatment from 48 to 96 weeks, did not show any significant improvement in sustained response rates[56]. In this study, the primary endpoint of undetectable HDV RNA at the end of therapy was not different between the two groups (peginterferon/tenofovir: 28/59 (48%) vs peginterferon/placebo: 20/61

(33%), p=0.12). Thus, given these various studies, the combination of nucleoside analogues with interferon does not seem to provide additional benefit in chronic HDV infection.

Past Investigational Therapies

Thymus-derived therapies

Thymosins and their synthetic derivatives are believed to induce T-cell differentiation and maturation, increase T cell function and restore immune defects. Given the early promising results in chronic HBV monoinfection[57, 58] in the early 1990s, it was explored in two small pilot studies for HDV.[59, 60] However, only 1 of 5 (20%) of patients became HDV RNA negative when treated with thymosin-alpha 1 900 ug/m^2 twice weekly for 6 months[60] and 3 of 11 became HDV RNA negative when treated with thymic humoral factor-gamma 2 (40 ug) when treated for 24 weeks with 2 of 3 demonstrating a virologic relapse. Since these early studies, further thymosin-focused investigation in HDV has not been described.

Current Investigational Therapies

Peginterferon Lambda-1a

Pegylated interferon lambda-1a is a type-III interferon that has demonstrated antiviral activity against HBV[61] and HCV[62]. Lambda's antiviral activity was first reported in *in vivo* models in 2006[63] and it has been described to utilize similar interferon-stimulated gene (ISG) induction pathways as interferon alfa thereby resulting in broad-spectrum antiviral activities and immunomodulatory properties. Lambda binds to type III interferon receptors which results in dimerization and activation of multiple intracellular signal transduction pathways mediated by the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. While this is similar to interferon alfa, a type-I interferon, type-III interferon lambda receptors are restricted to cells of epithelial origin which includes the liver.[64] Thus, initial clinical trials of peginterferon lambda in HBV and HCV demonstrated similar antiviral effects to peginterferon alfa, but demonstrated a substantially improved tolerability profile compared to peginterferon alfa.

In HDV, lambda interferon has demonstrated antiviral activity in *in vivo* human liver chimeric mouse models.[65] In humans, one study evaluating peginterferon lambda monotherapy in 33 chronic HDV patients has recently completed with the end of study results presented in first half of 2019.[66] In this randomized, open-label, multicenter study, peginterferon lambda was administered at doses of 120 or 180 ug weekly for 48 weeks. The end of study report has again confirmed that tolerability is improved compared to historical peginterferon alfa data and that both doses of peginterferon lambda have antiviral activity against HDV. Notably, in the high dose group, 9/14 (64%) of patients achieved either a 2 $\log_{10}$ decline in HDV RNA or had levels below the limit of quantification (BLOQ) at the end of therapy which was sustained in 7/14 (50%) of patients 24 weeks after therapy. Additionally, 5/14 (36%) of patients demonstrated a durable virologic response after 24 weeks of therapy (i.e. HDV RNA negative at EOT and 24 weeks post treatment). Given these promising results, peginterferon lambda's improved tolerability may be an attractive option for treating HDV, either as a monotherapy or in combination with other experimental

therapies. Currently, an open-label clinical trial exploring lambda interferon in combination with lonafarnib (LNF) (see below) and ritonavir (RTV) for 24 weeks in 26 patients is being evaluated at the National Institutes of Health Clinical Center ().

HBV/HDV entry inhibitors

Bulevirtide (Myrcludex B), a once daily subcutaneous injection, is a first-in-class HBV and HDV entry inhibitor that targets the human sodium-taurocholate co-transporter peptide (hNTCP) transmembrane protein. (Figure 1) The essential factor for receptor binding is the 47 N-terminal amino acids of the preS1 domain or the L-HBsAg envelope protein[67] and competitive binding to hNTCP by Bulevirtide , a myristolytated peptide that includes this N-terminal sequence, has demonstrated entry inhibition by HBV and HDV in *in vitro* and *in vivo* models.[32, 68, 69] In an early phase 2, randomized, 3-arm, open-label clinical study, 24 HDV patients were treated with Myrcludex B (2mg SQ daily) in combination with peginterferon alfa or Myrcludex B alone or Peginterferon alone for 24 weeks.[70] While the primary endpoint in this study, change in serum HBsAg levels, was not achieved, patients that received Myrcludex B experienced significant declines in serum HDV RNA and ALT levels. Notably, the combination of Myrcludex B and peginterferon group experienced mean HDV RNA declines of 2.6 $\log_{10}$ IU/L, the Myrcludex B monotherapy group had a 1.67 $\log_{10}$ IU/L, and the peginterferon group had a 2.2 $\log_{10}$ IU/L decline. HDV RNA became negative in 2 of 8 patients in both the Myrcludex B and peginterferon monotherapy groups and 5 of 7 patients in the combination therapy group. Myrcludex B was reported to be generally well tolerated in this study.

Since this study, a multicenter, open-labeled, randomized, phase 2b clinical trial further exploring the safety and efficacy of Myrcludex B has been performed in 120 HDV patients. Patients were randomized to subcutaneous daily injectable doses of Myrcludex B (2, 5, 10 mg) with oral tenofovir (245 mg/day) for 24 weeks. The primary endpoint of this study was a 2 $\log_{10}$ HDV RNA reduction or negativity in serum. Current end-of-study reports have described median HDV RNA declines in a dose dependent manner, ranging from 1.6 to 2.7 $\log_{10}$ IU/L, with Myrcludex B 10 mg demonstrating the greatest effect.[71] Additionally, ALT normalization was seen in up to 50% of patients. HDV RNA relapse occurred in all groups in up to 80% of subjects who responded to Myrcludex B therapy by 12 weeks of follow-up.

Additional studies exploring Bulevirtide in combination with peginterferon alfa is ongoing in Russia (). This multicenter, randomized, open-label phase 2 study is being performed to fUrther investigate the efficacy and safety of Bulevirtide alone and in combination with peginterferon in HDV patients. In this study, 90 patients are anticipated to be randomized into one of six arms: Bulevirtide (subcutaneous injection of 5 mg daily or 5 mg twice daily or 10 mg daily) with peginterferon alfa for 48 weeks, or subcutaneous injection of Bulevirtide 10 mg with Tenofovir for 48 weeks, subcutaneous injection of Bulevirtide 2 mg monotherapy for 48 weeks, or peginterferon alfa monotherapy for 48 weeks. The primary endpoint of this study is the achievement of undetectable HDV RNA by PCR 24 weeks after the end of therapy.

In April of 2019, two additional clinical trials are expected to begin further exploring Bulevirtide. The first is a multicenter, open-label randomized phase 2b clinical trial that will

likely enroll 175 patients from Russia, France, Moldova and Romania (). Patients will be randomized to one of four groups: Bulevirtide subcutaneous injection 2mg/day with peginterferon alfa for 48 weeks followed by Bulevirtide 2mg/day subcutaneous injection monotherapy for an additional 48 weeks, subcutaneous injection of Bulevirtide 10 mg/day with peginterferon for 48 weeks followed by subcutaneous injection of Bulevirtide 10 mg/day monotherapy for an additional 48 weeks, subcutaneous injection of Bulevirtide 10 mg/day monotherapy for 96 weeks, or peginterferon alfa for 48 weeks. All groups will then undergo 48 weeks of post-therapy follow-up. The primary endpoint of this study is undetectable HDV RNA in serum 24 weeks after the end of treatment.

The second study is a multicenter, open-label, randomized phase 3 clinical trial anticipated to begin assessing the long-term efficacy and safety of Bulevirtide in patients with HDV (). This three-arm study is estimated to enroll 150 HDV patients with randomization to: observation for 48 weeks followed by therapy with subcutaneous injection of Bulevirtide 10 mg/day for 96 weeks, subcutaneous injection of Bulevirtide 2 mg/day for 144 weeks, or subcutaneous injection of Bulevirtide 10 mg/day for 144 weeks. At the completion of therapy, all groups will undergo 96 weeks of additional follow-up. The primary endpoint of this study is the achievement of undetectable HDV RNA or a ≥ 2 $\log_{10}$ decline from baseline and ALT normalization at 48 weeks of therapy. The rationale for this extended treatment comes from modeling studies that suggest that at least three years continuous treatment with Bulevirtide might be needed to achieve sustained HDV RNA responses.

Given these early results, Bulevirtide has received orphan drug designation for the treatment of HDV infection from the European Medicines Agency (EMA) and from the U.S. Food & Drug Administration (FDA). Additionally, the EMA has granted Bulevirtide priority medicines (PRIME) scheme eligibility and the FDA has granted it breakthrough therapy designation. Interestingly, the appearance of antibodies to Bulevirtide has been demonstrated in some patients from the phase 2 studies; its significance is unknown and further evaluation is ongoing.[70] A recent study evaluating *in vitro* and *in vivo* models of the impact of cell proliferation on HDV persistence demonstrated that even with hNTCP blockage by myrcludex B, clonal cell expansion permitted amplification of HDV infection which resulted in HDAg- positive hepatocytes to be observed in dividing cells during all study timepoints.[72] Finally, the administration of Bulevirtide in healthy volunteers resulted in total plasma bile acids increases by 19.2 fold along with up to 124-fold increase in taurocholic acid, and an inhibition of uptake transporters OATP1B1 and OATP1B3 cytochrome P450 3A activity.[73, 74] However, the clinical importance of these findings have yet to be completely understood.

HBsAg secretion inhibitors

Nucleic acid polymers (NAPs) are phosphorothioated oligonucleotides with demonstrated broad-spectrum activities against various infectious agents including herpes simplex viruses, hepatitis B and C virus, and human immunodeficiency virus.[75-79] NAPs are hypothesized to have antiviral effects through several mechanisms including blocking viral entry which is dependent upon NAPs' phosphorothioation/amphipathicity that can interact with hydrophobic surfaces of proteins glycoproteins[78, 80], inhibition of HBsAg release[79, 81],

reduction of intracellular HBsAg via inhibition of subviral particle assembly[82], and possibly interactions with the SHDAg and LHDAg leading to inhibition of the HDV replication cycle (Figure 1).[83]

In human clinical studies, REP 2139-Ca is the lead NAP that has been investigated in HDV infected patients and is given as a once a week intravenous infusion. In a phase 2, proof-of-concept study () treating 12 patients with REP 2139-Ca monotherapy for 15 weeks weekly IV followed by combination therapy of half dose REP 2139-Ca given weekly IV with peginterferon-alfa for 15 weeks, and then peginterferon-alfa monotherapy for 33 weeks, REP 2139-Ca demonstrated antiviral effects against both HBV and HDV.[84] REP 2139-Ca appears to be the only one of the investigative therapies to reduce HBsAg rapidly resulting in a 3.5 $\log_{10}$ IU/ml decline in HBsAg from baseline.[84] A similar reduction was also seen in a prior safety and tolerability trial.[85] In patients who experienced a rapid decline in HBsAg with REP 2139-Ca monotherapy, peginterferon alfa-2a appeared to yield a profound increase in anti-HBs concentration. Overall, 6 of the 12 patients achieved anti-HBs titers above 10 mIU/mL by the end of therapy. Moreover, 9 of 12 patients became HDV RNA negative in serum by the end of treatment with a mean HDV RNA decline of 5.34 $\log_{10}$ IU/L. Substantial HDV RNA reduction was present in patients who had smaller declines in HBsAg which further suggests that NAPs have more than one antiviral mechanism. Moreover, this effect appears persistent as the 5 patients who achieved functional control of HBV maintained this control through 18 months. In addition, the 7 of the 9 patients who became HDV RNA negative maintained their negativity.[86] A follow-up study () exploring the durability of these responses through 3 years of follow-up is currently ongoing.

REP2139-Ca is generally well tolerated.[84, 85] The most frequently reported side effects with REP 2139-Ca in the initial safety and tolerability study included mild fatigue, dyspepsia, anorexia, dysphagia, dysgeusia, and hair loss. Many of these symptoms were attributed to heavy metal exposure at the trial site and the effect of increased mineral elimination by phosphorotioated oligonucleotides. Similar findings were not described in the more recent trial excluding patients with heavy metal exposure.[84, 87] Commonly seen side effects from REP 2139-Ca in the phase 2 study included pyrexia, chills, thrombocytopenia, and leukopenia.[84] Asymptomatic, self-resolving, substantial AST and ALT flares were commonly seen in HBV mono-infected patients after reductions of HBsAg raises the possibility of propagating decompensation in patients with advanced liver disease.[85] Smaller flares were also seen in HBV/HDV co-infection.[84] This is concerning since interferon therapy, which is being studied in combination with REP 2139-Ca, can cause similar flares which prevents its use in decompensated cirrhosis.[85, 88-90] One patient in the phase 2 study required discontinuation of the drug due to elevation in ALT and bilirubin after introduction of peginterferon alfa-2a.[84] Thus far, cirrhotic patients have not been included in studies investigating REP 2139-Ca. However, these flares may potentially be therapeutic as it was described to result in HBV viral load reduction and may be evidence of reactivation of immune response in the liver.[85]

Although promising, the interpretation of the results from these trials are limited by the small size of the trials. While studies have been done with intravenous dosing of REP 2139-CA, a subcutaneous formulation, REP2139-Mg, is currently being tested in HBV and a

study in HDV is set to begin enrollment in Q3 2019.[91] Good patient tolerability of the subcutaneous formulation will be needed for drug sustainability. Finally, additional evidence of the interplay between interferon therapy and NAPs are needed to determine if there is in fact improved rates of functional control of both HBV and HDV with combination therapy.

Virus assembly inhibitors

As previously mentioned in the virology section, prenylation is the process of adding a farnesyl group to the cysteine of the CXXX-box of the LHDAg and is essential for HDV virion assembly.[39] Lonafarnib is an orally available farnesyltransferase inhibitor (FTI) that has been extensively studied in cancer[92] and progeria[93] which disrupts the process of prenylation and in HDV prevents proper interaction of LHDAg with HBsAg (Figure 1).[94] In 2014, a proof-of-concept, randomized, placebo-controlled study demonstrated that oral lonafarnib resulted in a dose dependent, significant reduction in serum HDV RNA levels compared to placebo.[95] The most common side effects of lonafarnib were noted to be GI-related including nausea, diarrhea, anorexia, and weight loss which was also dose dependent.

This study was followed by the LOWR (**LO**nfarnib **W**ith and without **R**itonavir) HDV-1, 2, 3, and 4 studies. Ritonavir, an inhibitor of CYP3A4 which metabolizes lonafarnib, was added to allow for the use of lower doses of lonafarnib compared to the proof-of-concept study thereby minimizing GI-related side effects in a manner akin to the drug boosting tactic used with highly active antiretroviral therapy (HAART) in HIV. [42, 143] LOWR HDV-1 was a 7-arm, parallel, open-label study of 15 patients that were treated for up to 12 weeks that proved that the combination of lonafarnib with ritonavir improved patient tolerability and achieved higher serum lonafarnib concentrations, and that the addition of peginterferon alfa-2a was possible for future trials.[96]

This was followed by LOWR HDV-2, a dose-optimization, open-label study of various combinations of lonafarnib with ritonavir with or without peginterferon alfa-2a for 12, 24, or 48 weeks in 55 patients.[97] At 24 weeks, a dose-dependent response was seen between all oral lonafarnib 25 mg twice daily vs. 50 mg twice daily, each with ritonavir 100 mg twice daily. Addition of peginterferon alfa-2a to either of these regimens demonstrated additive to synergistic effects. The most impressive results thus far with lonafarnib occurred in this study in the low dose lonafarnib groups (oral 25 or 50 mg twice daily) with low dose ritonavir (oral 100 mg twice daily) and peginterferon alfa-2a triple combination therapy. 8 of 9 patients achieved serum HDV RNA levels BLOQ or ≥ 2 $\log_{10}$ IU/L decline in serum HDV RNA by week 24. Patients in the 50 mg group experienced an impressive 3.81 $\log_{10}$ IU/L decline in HDV RNA at 24 weeks. Finally, LOWR HDV-3 and 4 were two additional dose-finding and titration studies that have been recently conducted.[98, 99] LOWR HDV-3 demonstrated that once a day lonafarnib of 50 mg with ritonavir had superior results compared higher doses of lonafarnib (75mg or 100mg) with ritonavir.[98] Meanwhile, LOWR HDV-4 described that dose escalation of up to lonafarnib 100 mg twice daily with ritonavir was feasible.[99]

It is reassuring that resistance has thus far not been reported with lonafarnib.[95, 96] Interestingly, in LOWR-1 and LOWR-2, a subset of patients who did not achieve HDV RNA negativity on treatment experienced post-treatment, “therapeutic”, ALT flares with resultant

HDV RNA negativity and ALT normalization.[96, 97, 100] In those patients who had a liver biopsy before starting treatment, follow up biopsy performed after lonafarnib associated flare and ALT normalization revealed regression of fibrosis.[101] Similar to NAPs, these findings need to be studied further in patients who are not at risk for decompensation. The main side effects in the LOWR HDV studies with the low doses of lonafarnib (25 mg or 50 mg orally twice daily) to be taken into the phase 3 registration study are mild to moderate GI-related, which can be symptomatically managed with antidiarrheals, proton pump inhibitors, or antiemetics.

Due to these results, lonafarnib has received orphan drug designation for the treatment of HDV infection from the EMA and from the U.S. FDA. In addition, lonafarnib in combination with ritonavir has been granted Breakthrough Therapy designation by the FDA and PRIME designation by the EMA for HDV infection. This has resulted in the first phase 3 for HDV, which is a randomized, placebo-controlled, trial named D-LIVR (**D**elta **L**iver **I**mprovement and **V**irologic **R**esponse) () studying lonafarnib with ritonavir with or without peginterferon alfa-2a in 400 patients, and which is expected to be fully enrolled by the end of 2019.

Finally, the above data have supported the initiation of the first combination study of two investigational agents for HDV. As previously mentioned, a smaller phase 2 open label study evaluating the combination of peginterferon lambda, lonafarnib and RTV is currently ongoing at the National Institutes of Health Clinical Center ().

Conclusion

Despite being discovered over 40 years ago and being known as the most severe form of chronic viral hepatitis, the availability of adequate treatment options continues to an ongoing issue in chronic HDV infection. Although peginterferon alpha can be used with limited efficacy, it is plagued by significant side effects that limits its routine use. Multiple promising investigative therapies are now in clinical trials targeting the ISG-induction pathways (peginterferon lambda), viral entry (Bulevirtide, REP2139-Ca), subviral particle assembly/secretion (REP 2139-Ca/REP 2139-Mg), and virus assembly (lonafarnib). In the near term, therapies for patients afflicted with this devastating disease will be through participation in clinical trials and the likely success story will require some form of combination therapy.

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KEY POINTS

- Hepatitis D infection represents the most serious form of viral hepatitis in humans.
- Pegylated interferon alfa therapy is currently the recommended therapy but has attenuated efficacy at the cost of substantial side effects.
- With increased understanding of HDV, several promising drugs (pegylated interferon lambda, lonafarnib, Bulevirtide, REP2139-Ca) have been developed to target various stages of the HDV life cycle.
- Clinical trials of combination therapy with investigative drugs and pegylated interferon are currently underway.

SYNOPSIS

Chronic hepatitis D (CHD) results from an infection with hepatitis B virus (HBV) and hepatitis D virus (HDV). CHD is the most severe form of human viral hepatitis. Current treatment options consist of interferon alfa, which is effective only in a minority of patients. The study of HDV molecular virology has resulted in new approaches to therapy that have entered clinical trials, the most advanced of which has entered phase-3 studies. These include the entry inhibitor Bulevirtide, the nucleic acid polymer REP 2139-Ca, the farnesyltransferase inhibitor lonafarnib, and pegylated interferon lambda. This review summarizes available data of these emerging therapeutics

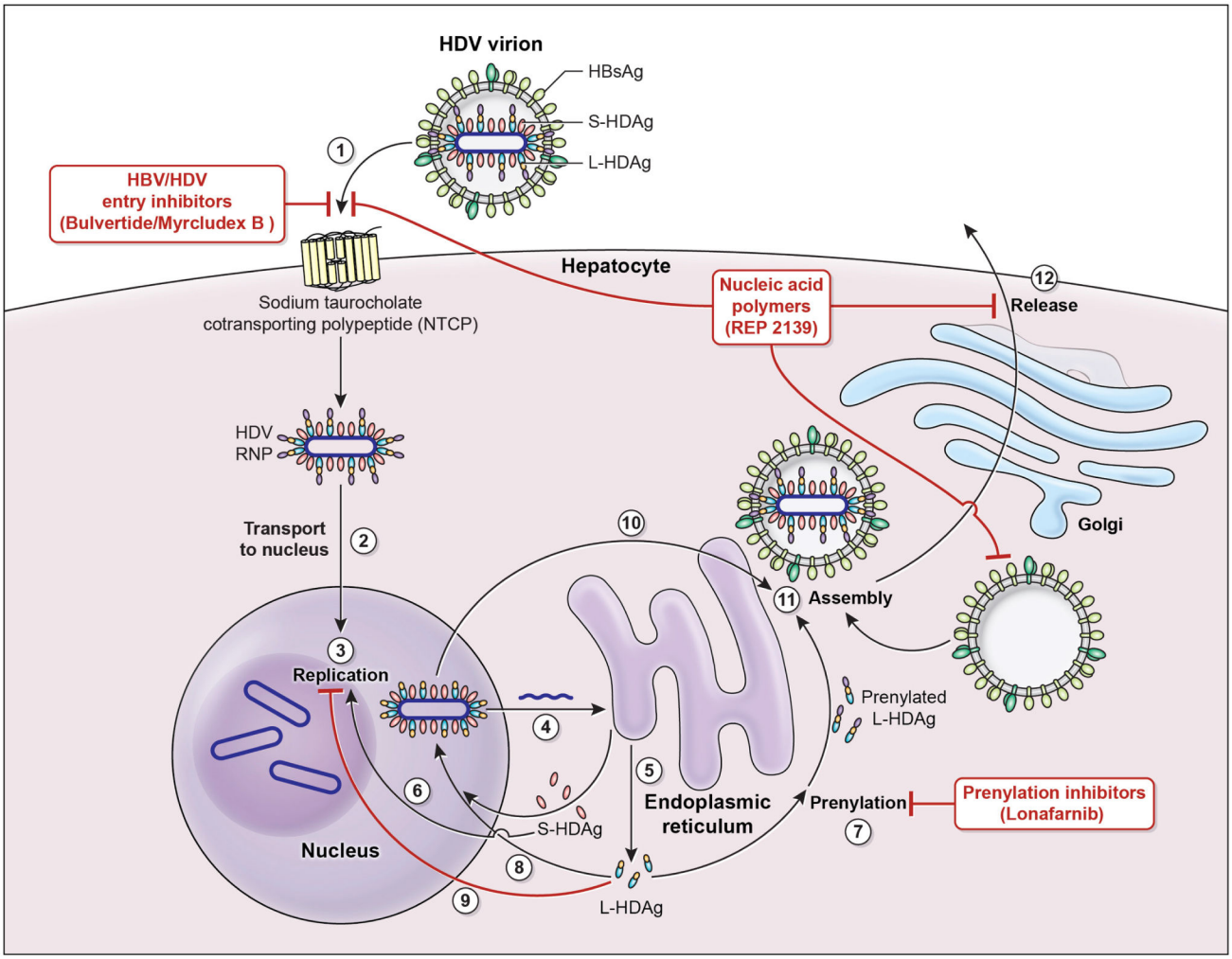

Figure 1. HDV viral life cycle and sites of investigative drug targets

1. Hepatitis D virus (HDV) virion attaches to the hepatocyte via interaction between Hepatitis B surface antigen proteins and the sodium taurocholate cotransporting polypeptide (NTCP).
2. HDV ribonucleoprotein (RNP) is translocated to nucleus mediated by the hepatitis D antigen (HDAg).
3. HDV genome replication occurs via a “rolling circle” mechanism.
4. HDV antigenome is transported out of the nucleus to the endoplasmic reticulum (ER).
5. HDV antigenome is translated in the ER into small HDAg (S-HDAg) and large HDAg (L-HDAg).
6. S-HDAg is transported into the nucleus.
7. S-HDAg promotes HDV replication in the nucleus.
8. L-HDAg undergoes prenylation prior to assembly.
9. L-HDAg inhibits HDV replication in the nucleus.
10. New HDAg molecules are associated with new transcripts of genomic RNA to form new RNPs that are exported to the cytoplasm.

11. New HDV RNP associates with Hepatitis B virus (HBV) envelop proteins and assembled into HDV virions.
12. Completed HDV virions are released from the hepatocyte via the trans-Golgi network.

Investigative drug and their targets:

HBV/HDV inhibitors (Bulvertide) - target the NTCP by competitive binding.

Nucleic acid polymers (REP 2139-Ca) – inhibits Hepatitis B surface antigen (HBsAg) and subviral assembly as well as HDV entry.

Prenylation inhibitors (Lonafarnib) – inhibits the process of prenylation of the L-HDAg which is the step leading up to assembly.