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HEPATITIS B (J LIM, SECTION EDITOR)

Update in Drug Development for Chronic HBV/HDV Infection

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Abstract

Purpose of Review Chronic hepatitis D is the most severe form of viral hepatitis. Currently, no drug has been approved for its treatment and pegylated interferon alpha remains the only recommended therapy, with dismal efficiency and important side effects. This review summarizes the recent advances in drug development for chronic hepatitis D.

Recent Findings A better knowledge of virology of hepatitis D virus has led to the development of several drugs targeting different steps of the viral life cycle. Among them, bulevirtide (a viral entry inhibitor, formerly denominated as Myrcludex B), lonafarnib (a viral assembly inhibitor), REP-2139-Ca (an inhibitor of HBsAg secretion), and pegylated interferon lambda have shown promising results in phase II clinical trials.

Summary In the near future, new therapeutic options will be available for the treatment of chronic hepatitis D. However, no drug is currently under development targeting viral replication and an effective treatment strategy may require combination of several drugs.

Keywords Chronic hepatitis D · Hepatitis D virus · Hepatitis B virus · Therapeutics · Clinical trials

Chronic Hepatitis Delta

Chronic hepatitis D or delta (CHD) results from the chronic infection of the liver by both hepatitis B and hepatitis D viruses (HBV and HDV). HDV, identified in 1977 by Rizzetto and colleagues, is the smallest of all known viruses and can only establish a productive infection in patients concomitantly infected by HBV [1]. In spite of being a defective virus, coinfection by HDV importantly aggravates the prognosis of HBV-infected patients and CHD is considered as the most severe form of chronic viral hepatitis, with a faster progression towards cirrhosis, an increased risk of hepatocellular carcinoma, and higher mortality in comparison to HBV monoinfection [2].

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The exact prevalence of HDV infection is still debated [3]. A recent estimation—albeit disputed—suggests that 62–72 million people are infected by HDV worldwide and argues that the real seroprevalence of the infection may have been widely underestimated [4••].

In high-resource settings, CHD has been classified as a rare disease and in Europe it is mostly restricted to intravenous drug users and migrants [5–7]. The same distribution has been observed in the USA, although recent statements suggest a much higher prevalence than previously estimated [8, 9].

In contrast, high prevalence regions include Eastern Europe, some countries of the Mediterranean basin and West Africa, patchy areas in the Amazon basin, the Western Pacific islands, and some Asian countries such as Pakistan, Afghanistan, and Mongolia (where HDV prevalence is as high as 60% of all HBsAg positive individuals) [10–13].

Hepatitis D Virus Life Cycle and Therapeutic Targets (Fig. 1)

HDV infection adds a layer of complexity to the already challenging management of patients chronically infected by HBV. Ideally, both viruses should be eliminated and successful strategies should lead to HBsAg clearance [14•]. The development

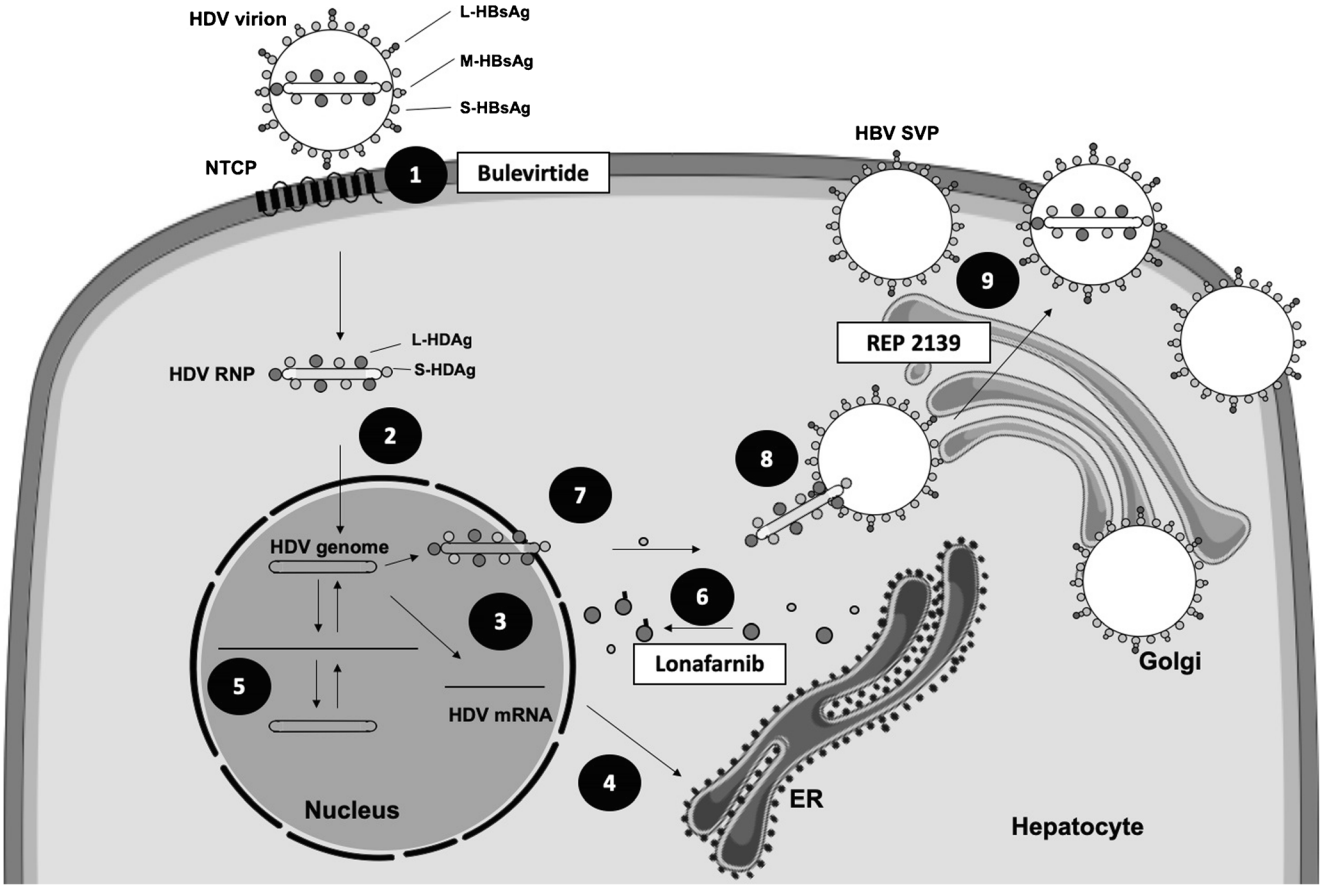

Fig. 1 HDV life cycle and targets for drugs undergoing clinical development. HDV entry (step 1) is dependent on the interaction between the myritoylated N-terminal residues of L-HBsAg at the surface of HDV virion and the viral receptor, NTCP, at the basolateral membrane of hepatocytes. This interaction is inhibited by bulevirtide. After entry into the cell, the RNP is transported into the nucleus (step 2). A small mRNA is transcribed from the viral genome by the host cell DNA-dependent RNA-polymerase II (step 3) and translated into HDAg at the endoplasmic reticulum (step 4). The viral genome is replicated through a double rolling circle mechanism, involving the synthesis of multimeric linear and antigenomic molecules and cleavage and ligation by the viral ribozyme (step 5). The farnesylation of L-HDAg is essential for the interaction of the RNP with the HBsAg (step 6). This step is inhibited by lonafarnib. Newly formed RNP are exported from the nucleus (step 7) and are enveloped by HBV surface proteins (step 8). The newly formed HDV virions are thought to be secreted through the Golgi, as the HBV SVPs (step 9). The antiviral activity of the NAP REP 2139 is thought to result both from an inhibition of HBsAg secretion and an interaction with HDAg. The mechanism of action IFN-lambda (not represented), as that of IFN-alpha, results from the expression of antiviral effector proteins, thought to inhibit several steps of the HDV cell cycle. Abbreviations: *ER*, endoplasmic reticulum; *HBV*, hepatitis B virus; *HDV*, hepatitis D virus; *IFN*, interferon; *NAP*s, nucleic acid polymers; *NTCP*, sodium taurocholate coreceptor peptide; *RNP*, ribonucleoprotein; *SVP*s, subviral particles

of such strategies implies a deep understanding of the viral cycles of both viruses and the interactions between them.

As mentioned before, HDV is the smallest known virus and is closely related to plant viroids [15]. The viral particle measures 35–37 nm and is composed of a ribonucleoprotein (RNP, formed during HDV replication, independently from HBV) and an envelope (provided by HBV) [16].

The HDV envelope is a lipoprotein structure formed upon viral egress from cells infected by both HDV and HBV. It contains the three forms of HBV surface proteins (HBsAg)—small (S-HBsAg), medium (M-HBsAg) and large (L-HBsAg)—which are essential for HDV virion assembly and entry into hepatocytes [17]. As for HBV, the interaction of the myristoylated N-terminus of the pre-S1 domain contained in L-HBsAg with NTCP (Sodium Taurocholate Cotransporting Peptide, the viral receptor, expressed at the basolateral membrane of hepatocytes) is essential for HDV viral entry [18].

In infected cells, the viral genome is translocated to the nucleus in association with the viral protein, in the form of a ribonucleoprotein. The HDV genome is a circular, covalently closed single-stranded RNA of ~1680 nucleotides, folded into a partially double-stranded rod-like structure, as a result of extensive, internal base pairing. It serves as a matrix for the transcription of a small messenger RNA from that allows

the expression of HDAg, HDV's only protein. HDAg has 2 isoforms—small or S-HDAg and large or L-HDAg—resulting from an editing event mediated by adenosine deaminase acting on RNA 1 (ADAR1) [19].

The HDV genome is replicated in the nucleus through a double rolling circle mechanism, involving the transcription of multimers by the cell DNA-dependent RNA polymerases (particularly RNA Pol II) and autocatalytic cleavage by a HDV ribozyme [20]. The virus detours RNA Pol II through a mechanism not fully elucidated to these very days, for which S-HDAg seems to be necessary [21, 22]. During viral replication, which is independent of HBV, no DNA intermediates or persistent forms are generated.

The interaction of newly formed genome molecules with both forms of HDAg (in the form of a RNP, as previously described) allows the assembly and secretion of viral particles, through the interaction of the farnesylated form of L-HDAg with HBsAg [23, 24].

From its replication cycle, it becomes clear that HDV depends on the host cell for its replication and on its helper virus for its propagation and does not possess any enzymatic activity that can be directly targeted by small molecules (as is the case for HBV's reverse transcriptase or HCV's polymerase and protease). Furthermore, although the viral replication induces an exuberant interferon response, it does not seem to be inhibited by this response, suggesting that it has developed resistance mechanism towards interferon [25, 26]. Taken together, these characteristics justify the remaining challenge to develop antiviral strategies against HDV.

Past and Current Therapeutic Strategies

A wide range of strategies has been tested for the treatment of HDV infection, including antiviral and immunomodulatory agents.

Nucleotide analogues used for the treatment of chronic hepatitis B (lamivudine, clevudine, adefovir, entecavir and tenofovir) fail to inhibit HDV replication, and so do ribavirin, acyclovir, and famciclovir [27]. Furthermore, in vitro trials of inhibition of HDV ribozyme have proven only moderately efficient and no further investigation of this possibility has been reported [28].

Immunomodulatory strategies, such as corticotherapy and thymus-derived therapies, were evaluated early during the study of the infection and have also proven inefficient [27].

Interferon-alpha (IFN-alpha, currently used on its pegylated form that allows weekly administration) remains the only recommended agent for the treatment of CHD (even though its use remains off-label) and current guidelines propose a treatment course of 48 weeks [29, 30]. Unfortunately, less than 30% of the patients achieve negativity of circulating HDV RNA 24 weeks after the end of treatment [31]. Furthermore, late relapses may occur in 56% of the responders, further reducing the impact of treatment and questioning the use of the 24-week post-treatment endpoint in CHD patients [32]. Other durations of treatment have been evaluated [33]. In particular, the prolongation of treatment duration to 96 weeks failed to increase efficacy [34••]. The addition of nucleotide analogues (either adefovir or tenofovir) also failed to improve outcomes [31, 34••].

Therapeutic Strategies in Clinical Development

Several factors hamper antiviral development targeting HDV. Firstly, the disease is considered to be rare, particularly in high-resource countries. Secondly, the evaluation of treatment response remains challenging by lack of standardized tools. Finally, clinical trials are difficult to conduct as most CHD patients are in advanced phases of disease and hence have a decreased tolerance to drugs.

Furthermore, although the goal of drug development for most viral infections is aimed at directly targeting replication, in the case of HDV, such approach is limited by the complete dependence of the virus on the host cell enzymes and lack of specific enzymatic activity. No direct-acting antiviral is currently in development—the drugs undergoing evaluation target either host cell mechanisms or the HBsAg secretion. Three of them (interferon lambda, lonafarnib, and bulevirtide) have received the orphan drug designation, intended to facilitate drug development and marketing (Table 1).

Pegylated Interferon Lambda

The antiviral activity of IFN-lambda (a type III interferon) stems from its ability to activate the same intracellular pathways than type I interferons (as interferon alpha), i.e., the JAK/STAT pathway, inducing the expression of similar interferon stimulated genes (ISGs) that code for antiviral effector proteins. Despite its similar mechanism of action and efficiency, type III interferons target a more restricted range of cells, resulting from a limited expression of their receptor—highly expressed in hepatocytes, but with limited expression in hematopoietic and central nervous system cells [35]. Hence, the rationale behind their use is justified by an expected better tolerability.

Data are already available for patients with chronic hepatitis B and C, where its antiviral activity was equivalent to pegylated IFN-alpha [35, 36].

Experiments in humanized mice have shown an antiviral activity against HDV that is similar to pegylated IFN-alpha [37•].

Table 1 Summary of the studies evaluating molecules in clinical development for chronic hepatitis D

Identification	Phase	Treatment arms	Duration	Number patients	Clinical trial number*
LIMT HDV	Phase 2	*Pegylated IFN-lambda 120 or 180 μg sc QW	48 weeks	33	NCT02765802
LIFT	Phase 2	*Lonafarnib + ritonavir with pegylated IFN-lambda	24 weeks	32	NCT03600714
MYR 201	Phase 1 and 2	*Bulevirtide 2 mg sc QD for 24 weeks, followed by pegylated IFN-alfa-2a 180 μg sc QW for 48 weeks *Bulevirtide 2 mg sc QD + pegylated IFN-alfa-2a 180 μg sc QW for 24 weeks, followed by pegylated IFN alfa-2a 180 μg sc QW for 24 weeks *Pegylated IFN-alfa-2a 180 μg sc QW for 48 weeks	72 weeks	24	NCT02637999
MYR 202	Phase 2	*Bulevirtide, 2 mg sc QD + tenofovir for 24 weeks, followed by tenofovir for 24 weeks *Bulevirtide, 5 mg sc QD + tenofovir for 24 weeks, followed by tenofovir for 24 weeks *Bulevirtide, 10 mg sc QD + tenofovir for 24 weeks, followed by tenofovir for 24 weeks *Tenofovir for 48 weeks	48 weeks	120	NCT03546621
MYR 203	Phase 2	*Bulevirtide 2 mg sc QD + pegylated IFN alfa-2a 180 μg sc QW for 48 weeks *Bulevirtide 5 mg sc QD + pegylated IFN alfa-2a 180 μg sc QW for 48 weeks *Bulevirtide 2 mg sc QD for 48 weeks *Pegylated IFN alfa-2a 180 μg sc QW for 48 weeks	48 weeks	60	NCT02888106
MYR 204	Phase 2b	*Bulevirtide 2 mg sc QD + pegylated IFN alfa-2a 180 μg sc QW for 48 weeks followed by Bulevirtide 2 mg sc QD for 48 weeks *Bulevirtide 10 mg sc QD + pegylated IFN alfa-2a 180 μg sc QW for 48 weeks followed by Bulevirtide 10 mg sc QD for 48 weeks *Bulevirtide 10 mg sc QD for 96 weeks * pegylated IFN alfa-2a 180 μg sc QW for 48 weeks	96 weeks	175	NCT03852433
MYR 301	Phase 3	*Observation for 48 weeks followed by Bulevirtide 10 mg sc for 96 weeks *Bulevirtide 2 mg sc QD for 144 weeks *Bulevirtide 10 mg sc QD for 144 weeks	144 weeks	150	NCT03852719
12-DK-0046	Phase 2a	*Lonafarnib 100 mg po BID for 4 weeks *Lonafarnib 200 mg po BID for 4 weeks *Placebo for 4 weeks	4 weeks	14	NCT01495585
LOWR HDV-1	Phase 2a	*Lonafarnib 200 mg po BID *Lonafarnib 100 mg po TID *Lonafarnib 100 mg po BID + pegylated IFN-a 180 μg sc QW *Lonafarnib 100 mg po BID + ritonavir 100 mg po QD	24 weeks	15	NCT02430181
LOWR HDV-2	Phase 2a	*High dose: Lonafarnib > 75 mg po BID + ritonavir *Low dose all oral: Lonafarnib 25 or 50 mg po BID + ritonavir 100 mg po BID Low dose triple combination: Lonafarnib 25 or 50 mg po BID + ritonavir 100 mg po BID + pegylated IFN-a 180 μg sc QW	12 to 48 weeks	58	NCT02430194
LOWR HDV-3	Phase 2a	*Lonafarnib/ Ritonavir 50 mg/100 mg po QD for 24 weeks *Lonafarnib/ Ritonavir 75 mg/100 mg po QD for 24 weeks *Lonafarnib/ Ritonavir 100 mg/100 mg po QD for 24 weeks *Placebo for 12 weeks followed by Lonafarnib/ Ritonavir 50 mg/100 mg po QD for 12 weeks *Placebo for 12 weeks followed by Lonafarnib/ Ritonavir 75 mg/100 mg po QD for 12 weeks *Placebo for 12 weeks followed by Lonafarnib/ Ritonavir 100 mg/100 mg QD for 12 weeks	24 weeks	22	NCT02511431
LOWR HDV-4	Phase 2	Lonafarnib starting at 50 mg bid in combination with ritonavir 100 mg po BID and escalating to lonafarnib 75 mg po BID and then 100 mg po BID as tolerated.	6 months	15	NCT02527707
D-LIVR	Phase 3	*Lonafarnib 50 mg po BID + Ritonavir 100 mg po BID *Lonafarnib 50 mg po BID + Ritonavir 100 mg po BID + pegylated IFN alfa-2a 180 mcg QW *Placebo lonafarnib + placebo ritonavir + pegylated IFN alfa-2a 180 μg QW	48 weeks	400	NCT03719313
REP 301	Phase 2	*REP 2139-Ca 500 mg iv QW for 15 weeks followed by REP 2139-Ca 250 mg iv QW + pegylated IFN alfa-2a 180 μg QW for 15 weeks followed by pegylated IFN alfa-2a 180 μg QW for 33 weeks	63 weeks	12	NCT02233075

Abbreviations: *BID*, twice a day; *IV*, intravenous; *PO*, per os; *QW*, weekly; *QD*, daily; *SC*, subcutaneous; *TID*, three times per day

*www.clinicaltrials.gov

Pegylated IFN-lambda is currently being evaluated in phase II clinical trials both in monotherapy and in combination with the prenylation inhibitor lonafarnib.

Results of the first study (LIMT HDV study) were presented at the EASL meeting in 2019 [38]. In this study, 33 patients with CHD were randomized to receive either 120 or 180 μg of pegylated IFN-lambda per week in monotherapy for 48 weeks. At 24 weeks after the end of treatment, 36% (5/14) of the patients treated with high-dose IFN-lambda and 16% (3/19) of in the low-dose arm kept HDV RNA levels below the limit of quantification (values comparable to historical cohorts of alpha), with a better safety profile.

Patients are currently being recruited for a second study (LIFT; NCT03600714) that aims to evaluate the combination of pegylated IFN-lambda with lonafarnib and ritonavir (discussed below).

Viral Entry Inhibitors

Bulevirtide

Bulevirtide (previously designated Myrcludex B) efficiently inhibits viral entry for both HBV and HDV and its development results from the study of viral and host determinants for the entry of both viruses.

As stated before, the entry of both HBV and HDV in hepatocytes depends on the interaction of their shared viral envelope with NTCP on the basolateral membrane of the host cell. More specifically, this interaction is mediated by the myristoylated 75 N-terminal amino acids of the preS1 domain of L-HBsAg [39, 40]. Bulevirtide is a synthetic myristoylated peptide mimicking the N-terminal 47 amino acids of the preS1 domain. It has been shown to potently and specifically inhibit both HBV and HDV entry in vitro and in vivo [41, 42]. Encouraging results obtained in the humanized mouse model indicate that, over time, bulevirtide therapy is associated with a linear decline in the number of HDV infected hepatocytes, suggesting that prolonged treatment courses may lead to eradication of the infection (although a clear demonstration is still missing) [43].

Bulevirtide's binding to NTCP efficiently inhibits viral entry (IC50 80 pmol/ L) at doses that should not interfere with bile acid transport (IC50 47 nmol/ L) [44].

Subsequent studies focused on bulevirtide efficacy in CHD. A first, proof of concept phase Ia/IIb clinical trial (MYR 201; NCT02637999) included 24 patients and evaluated the efficiency of bulevirtide treatment, either in monotherapy or in association with pegylated IFN-alpha for 24 weeks, followed by pegylated IFN-alpha monotherapy. Although important reductions of HDV RNA levels were observed at the end of bulevirtide treatment (up to 2.6 log10 in the combination arm) and seven patients attained HDV RNA levels below the level of quantification, no impact on HBsAg levels (the primary endpoint of the study) was documented and viral rebound was universal after treatment cessation [45••].

A larger phase IIb study followed (MYR 202; NCT03546621), including 120 patients pretreated with tenofovir, evaluated several doses of bulevirtide (2, 5, and 10 mg) in combination with tenofovir for 24 weeks. A dose-dependent decrease in HDV RNA was observed, ranging from 1.6 to 2.7 log10 (in the 10 mg arm), again with a rebound after treatment cessation [46].

Promising results of a more recent phase II study (MYR 203; NCT02888106), including 60 patients and evaluating a 48-week of bulevirtide (2 and 5 mg) in combination with pegylated IFN-alpha, in comparison to either monotherapy, were reported in April 2019. At 72 weeks (24 weeks after the end of treatment), 40% of the patients in the combination arms (12/30) had undetectable HDV RNA and 13% (4/30) lost HBsAg. Interestingly, the 2-mg arm outperformed the 5-mg arm, as had already been observed in MYR-202 [47]. Although serum bile salt elevations were observed, these were asymptomatic and did not require bulevirtide dose adjustments.

Recruitment has started in February 2019 for an additional phase II, multicentric trial, expected to enroll 175 patients (MYR 204; NCT03852433) and aimed to evaluate the efficacy and safety of a 96-week treatment course with bulevirtide (2 and 10 mg), in combination with pegylated IFN-alpha for 48 weeks and compared to either drug alone.

Recruitment is also ongoing for a phase III study (MYR 301; NCT03852719) aiming to enroll 150 patients in order to assess the efficacy and safety of a 144-week course of bulevirtide (2 and 10 mg).

Although an oral formulation is under development, daily subcutaneous injections are currently needed [48].

Virus Assembly Inhibitors

Lonafarnib

HDV assembly is dependent on the interaction between the farnesylated form of L-HDAg and HBsAg. Farnesylation (a type of prenylation) consists in the addition of a farnesyl group to the CXXX box at the C-terminus of L-HDAg by a cellular farnesyltransferase [24]. This reaction allows the migration of the RNP complex into the endoplasmic reticulum and its interaction with the S domain of HBsAg [49]. Hence, inhibition of the cellular farnesyltransferases hinders HDV assembly and viral particle secretion cannot take place [23].

Farnesyltransferase inhibitors, initially evaluated as anticancer drugs, have been shown to inhibit HDV secretion both in vitro and in vivo [23, 50].

Lonafarnib is a farnesyltransferase inhibitor, available as an oral formulation and has demonstrated anti-HDV activity in a 2014 phase IIa study (NCT01495585). In this placebo-controlled proof of concept study including 14 patients, lonafarnib (100 or 200 mg twice daily) was administered daily for 4 weeks and led to a dose dependent decline of HDV RNA at the end of treatment (up to 1.54log10 in the 200 mg arm) [51]. Gastrointestinal adverse events were however common.

A subsequent phase II study (LOWR HDV-1; NCT02430181) enrolled 15 patients and compared lonafarnib in monotherapy and in combination with pegylated IFN-alpha or ritonavir (a CYP3A4 inhibitor, aimed to allow a dose reduction of lonafarnib, thus increasing its tolerability). Addition of ritonavir to lonafarnib 100 mg bid yielded better antiviral responses than lonafarnib 300 mg BID monotherapy (2.4 log10 versus 2 log10 decrease at 4 weeks of treatment), with less side effects [52••].

The following studies LOWR HDV-2, 3, and 4 (NCT02430194, NCT02511431 and NCT02527707, respectively) were aimed at optimizing dose and treatment duration, using combinations of lonafarnib and ritonavir with pegylated IFN-alpha [53–55]. The best results thus far were obtained in the LOWR HDV-2 study, where the combination of lonafarnib 25 mg BID, ritonavir 100 mg BID, and pegylated IFN-alpha for 24 weeks led to a median HDV RNA decrease of 5.57log10 at the end of treatment [53]. Gastrointestinal side effects, although milder at lower doses of ritonavir potentiated lonafarnib, are still an issue for this treatment.

A phase III study (D-LIVR; NCT03719313) is currently recruiting with the goal of including 400 patients randomized into 4 arms, including a lonafarnib 50 mg BID with ritonavir 100 mg BID with or without pegylated IFN-alpha in comparison to pegylated IFN-alpha monotherapy and placebo.

As mentioned before, a phase II trial evaluating a combination of lonafarnib/ritonavir with pegylated IFN-lambda is currently ongoing (LIFT; NCT03600714).

Nucleic Acid Polymers

Nucleic acid polymers (NAPs) are phosphorothioate oligonucleotides, whose broad spectrum of antiviral activities stems from their ability to interact with hydrophobic surfaces of proteins, in a sequence-independent manner [56]. An antiviral effect has previously been demonstrated against human immunodeficiency virus, hepatitis C virus and herpes simplex virus [57–59]. Such an effect has also been documented for HBV and, although the precise mechanisms of action are not entirely clear, their anti-HBV activity is considered to result from the inhibition of HBsAg secretion from hepatocytes [60]. In HDV infection, besides the effects on HBsAg secretion, an additional mechanism may involve a direct interaction of NAPs (in particular REP 2139) with HDAg [61].

In a first proof of concept uncontrolled phase II trial (REP 301; NTC02233075), 12 CHD patients were treated with REP 2139-Ca in monotherapy for 15 weeks, followed by a combination of REP 2139-Ca and pegylated IFN-alpha for another 15 weeks and finally pegylated IFN-alpha in monotherapy for 33 weeks. Striking declines in HBsAg were observed at the end of combination therapy, with 50% (6/12) of patients seroconverting to anti-HBs and 75% (9/12) having serum HDV RNA levels below the limit of detection [62••]. Furthermore, these effects partially persisted up to 18 months after treatment cessation, when 7 of the 9 patients who had achieved HDV RNA undetectability at the end of treatment remained negative and 5 patients still maintained HBsAg negativity [63].

Transaminase flares have been documented in roughly half of the HBV and HDV infected patients treated with REP 2139-Ca. With the exception of one patient, they were clinically silent and self-resolving and may be associated with the resolution of the infection(s) by the immune system [64]. However, the impact these flares may have in patients with advanced disease is still to be determined.

Given the promising results of the previous small studies, larger trials are expected to establish the safety and efficacy of this treatment. Furthermore, a new formulation of REP 2139 (REP 2139-Mg), allowing a weekly subcutaneous administration is being developed, in order to reduce the constraints of the intravenous administration of the currently available REP 2139-Ca. It will be evaluated for the treatment of chronic hepatitis B (REP 401; NCT02565719) and a trial of this molecule in combination with pegylated IFN-alpha and tenofovir on CHD is being planned [65].

Conclusion and Perspectives

More than 40 years after the identification of HDV, its infection still poses important challenges both from a clinical and biological perspective. Indeed, despite its severity, its real impact worldwide is still debated, and therapeutic options are limited.

Important contributions to the knowledge of HDV virology, as the identification of its host cell receptor less than one decade ago, have contributed to the development of promising therapeutic strategies that are currently undergoing clinical evaluation. The classification as some of the new drugs as orphan is expected to accelerate the development phase and allow an earlier availability. Furthermore, the efforts currently being allocated to the perspective of an HBV cure are expected to have an impact on HDV infection and it can be speculated that therapeutic strategies as immunomodulation and RNA interference may be used to treat the infection by both viruses.

It is likely that a combination of several drugs will be needed to target HDV infection and in the absence of a currently available strategy to directly inhibit viral replication, the quest for a better understanding of the mechanisms of HDV infection must continue.

Acknowledgements Elements used in the figure were adapted with permission from Servier Medical Art (license: https://creativecommons.org/licenses/by/3.0/fr/).

Compliance with Ethical Standards

Conflict of Interest Dulce Alfaiate declares no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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