ENDPOINTS AND NEW OPTIONS FOR TREATMENT OF CHRONIC HEPATITIS D

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List of abbreviations: IFNα, interferon alfa; CHD, chronic hepatitis D; HDV, hepatitis D virus; HBV, hepatitis B virus; SVR, sustained virologic response; pegIFNα, pegylated interferon alfa; NTCP, Sodium Taurocholate Co-transporting Polypeptide; NAP, nuclei acid polymer; LNF, lonafarnib; BLV, bulevirtide; TDF, tenofovir disoproxil fumarate; pegIFNλ, pegylated interferon lambda.

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Abstract

Therapy of chronic hepatitis D still relies on interferon alfa. However, efficacy is limited and better therapies are needed. Disruption of the interactions of HDV with the helper HBV or with the host is providing a new therapeutic paradigm and new treatment options are investigated. The evaluation of efficacy is made difficult by the lack of robust virologic end-points of therapy and the management of chronic hepatitis D is challenging. This article provides a critical review of the results so far obtained with the new antivirals against the Hepatitis D Virus in advanced stages of development and summarizes the problems and perspectives of their clinical use.

Efficacious, simple and well tolerated therapies are available to control hepatitis B and to cure hepatitis C but such therapies are not yet available for hepatitis D. The time-honored interferon alfa (IFN□) remains the only therapy for chronic hepatitis D (CHD) (1). Although hepatitis D virus (HDV) induces liver disease only in the setting of a dual infection with HBV, attempts to control CHD by inhibiting replication of the hepatitis B virus (HBV) with nucleos(t)ide analogues were of no avail.

Targets for new HDV therapies

The reason why HDV is refractory to conventional antiviral therapies lies in its unique structure and biology (2). The HDV genome (1.7 kb) is too small to code for the proteins required for its own replication and instead relies on the replicative machinery of the hepatocyte, requiring from HBV only the HBsAg to enter liver cells and to disseminate infection. Thus, HDV replication cycle is not affected by conventional medications that directly target common viral replication processes, such as the viral polymerase inhibitors used in HBV and Hepatitis C Virus infections.

New strategies target interactions of HDV with HBsAg or the infected host, in order to deprive the virus of extrinsic functions critical to its replication cycle (1, 3). In this review, we will discuss endpoints of CHD treatment and review the efficacy of new therapies in clinical trials.

Endpoints for CHD treatment

Similar to chronic Hepatitis C, IFNα trials for CHD considered undetectable HDV RNA six months after the end of therapy, as evidence of “sustained virologic response” (SVR) and successful

therapy (1). Reported SVR rates are generally low, i.e., ~25-30%, and late relapses are common. In a 10-year follow-up of the HDTI trial of pegylated IFNα (pegIFNα) with or without adefovir dipivoxil, 8 of 14 (57%) CHD patients who had achieved SVR experienced a virologic relapse (4). The high rate of HDV relapse is not surprising, considering the limited sensitivity of current diagnostic assays for serum HDV RNA with lower detection limit around 15 copies/ml, corresponding to approximately 930 IU/ml (5, 6). Thus HDV is likely still present in the liver despite undetectable serum HDV RNA and viral relapse can occur as long as HBV is also present; integration of HBV in the host genome may also contribute to the production of the HBsAg required for HDV morphogenesis (2). Indeed, the term SVR is never used in patients with chronic hepatitis B receiving nucleos(t)ide analogues, as viral relapse is near universal when treatment is discontinued even after many years of undetectable serum HBV DNA.

Given the low rate of "SVR" and the high rates of late virologic relapse with IFNα therapy, alternative endpoints need to be considered in assessing efficacy of new CHD therapies. These endpoints need to be shown to be associated with clinical benefit, such as biochemical or histological improvement or decreased risk of cirrhosis, decompensation or hepatocellular carcinoma. From one small study showing an association of HDV decline with survival benefit (7), a ≥2 Log reduction in serum HDV RNA from baseline was proposed by an expert panel (8) as initial treatment efficacy in clinical trials for CHD. However, subsequent studies have used this criterion as an off-treatment endpoint of therapeutic efficacy. This is problematic as it does not consider the baseline HDV RNA level; thus, HDV RNA levels below detection after treatment and levels of 10E05 IU/mL (decreased from >10E07 IU/mL) would both be considered to have met therapeutic endpoint. Furthermore, it assumes that serum HDV RNA levels at the end of treatment can be sustained after discontinuation of treatment or that treatment can be continued in the long-term in order to maintain the potential for clinical benefit. However, the practicality of long-term therapy will depend on safety, ease of administration and costs of the medications used. An alternative endpoint may be a decrease in serum HDV RNA below a certain level, similar to inactive carriers in chronic hepatitis B (9), but the threshold level of HDV RNA for clinical benefit has not been defined.

The ideal endpoint of CHD treatment would be HBsAg loss, similar to the proposed definition for functional HBV cure. This is rarely achieved with IFNα monotherapy; whether combination of new therapies in development will increase the rate of HBsAg loss remains to be determined.

New targets for HDV treatment

Several new targets have been identified for drug development against HDV. Of these, three have been tested in clinical trials (**Figure 1**).

1) HBsAg secretion inhibitor - REP-2139 is a nucleic acid polymer that interacts with a host chaperone, blocking the assembly/release of subviral HBsAg particles. Since subviral particles account for >99.99% of HBsAg in the circulation, REP-2139 might reduce available HBsAg to support HDV particle assembly. Modeling estimates also suggest an accelerated loss of HDV-infected cells *via* hitherto unknown mechanisms (10).
2) Farnesyl-transferase inhibitor – Lonafarnib (LNF), interferes with the assembly of HDV virion, which requires farnesylation by the host of the large HDAg isoform of the virus (11).
3) Entry inhibitor - Bulevirtide (BLV, formerly Myrcludex B), a small myristoylated synthetic lipopeptide corresponding to the HBV preS1 sequence, blocks the binding of HBsAg-enveloped particles to Sodium Taurocholate Co-transporting Polypeptide (NTCP), the entry receptor for both HBV and HDV, preventing entry of HDV into hepatocytes (12).

The therapeutic potential of all three strategies has been shown in phase 2 trials (13-15), and LNF and BLV are moving into phase 3 trials.

Efficacy in clinical trials

HBsAg secretion inhibitor

A small study of REP 2139-Ca given for 15 weeks as monotherapy, followed by add-on pegIFNα for 15 weeks and then pegIFNα monotherapy for another 33 weeks in 12 CHD patients, found that at the end of therapy seven patients had undetectable HDV RNA and five had cleared HBsAg (13). After 3.5 years follow-up, 7 of 11 patients had undetectable HDV DNA and 4 had HBsAg loss (16). Further studies are needed to confirm these impressive response rates.

Farnesyl-transferase inhibitor (Table 1)

A pilot trial showed that LNF monotherapy, given orally, decreased serum HDV RNA levels but all patients experienced gastrointestinal side effects. Subsequent studies assessed split doses as well as combination with the cytochrome P450 3A4 inhibitor ritonavir to allow for lower doses of LNF while preserving its antiviral activity. The best results with this dual combination were reported in the LOWR-2 study (17) where HDV RNA fell below the detection limit in 5 of 13 patients assigned to receive LNF 50 mg bid with ritonavir 100 mg bid for 24 weeks. Varying doses of LNF from 50 to 100 mg plus ritonavir 100 mg qd were studied in LOWR-3 (18) and gradually escalating doses of

LNF from 50 to 100 mg bid plus ritonavir 100 mg bid were studied in LOWR-4 (19). Higher doses of LNF were associated with more adverse effects. For the LIFT-HDV study, LNF 50 mg bid and ritonavir 100 mg bid were combined with pegylated interferon lambda (pegIFNλ) at weekly doses of 180 μg for 24 weeks (20). Serum HDV RNA became undetectable at the end of treatment in 11 of 26 patients, with 5 maintaining their response 24 weeks after the end of therapy, but none lost HBsAg. In contrast to IFNα, IFNλ has less side effects. PegIFNλ monotherapy has also been shown to be efficacious in the LIMT study (21), where 5 of 14 patients had undetectable HDV RNA at the end of 48 week treatment and at 24 week follow-up. In the ongoing phase 3 D-LIVR study, LNF plus ritonavir are combined with pegIFNα for 48 weeks. In view of the need for long-term therapies, it is likely that the side effects of LNF, though mitigated by ritonavir, may remain a concern, particularly when added to those of pegIFNα.

Entry inhibitor (Table 2)

Bulevirtide has been studied as monotherapy and in combination with pegIFNα and/or tenofovir disoproxil fumarate (TDF). It is administered daily by the subcutaneous route and is generally well tolerated despite a dose-dependent bile acid increase.

In the MYR 202 trial (22), 90 patients received TDF for 12 weeks followed by BLV (2, 5 or 10 mg) plus TDF for 24 weeks, and then TDF for 24 weeks, while 30 patients received TDF monotherapy for 60 weeks. HDV RNA decrease by ≥2 Log (or undetectable) was observed in 46-77% patients at the end of BLV therapy, with the highest response rate in the group that received BLV 10 mg doses. However, at the end of FU (i.e. 24 weeks after the end of BLV therapy) 7-10% of patients had maintained these HDV responses. Three patients lost HBsAg (1 in the BLV 2 mg group and 2 in the 5 mg group but none in the 10 mg group) while none of the patients in the TDF monotherapy group had HDV RNA or HBsAg response.

In the MYR 203 study (23, 24), 90 patients were enrolled into 6 groups (15 patients each) of 48 week treatment. The primary endpoint of undetectable HDV RNA at week 72 was achieved in 8 (53%), 4 (27%) and 1 (7%) patients who received combination of pegIFNα and 2, 5, and 10 mg BLV, respectively, compared to 1 (7%) patient who received 2 mg BLV monotherapy, none who received pegIFNα monotherapy and 3 (33%) who received 10 mg BLV and TDF. At week 72, ≥1 Log decrease in HBsAg was observed only in patients who received combination of pegIFNα and BLV with the highest response in those who received BLV 2 mg doses but not in those who received

BLV or pegIFNα monotherapy or combination of BLV and TDF. HBsAg became undetectable in 4/15 of patients treated with pegIFNα and BLV 2 mg.

Results of MYR 202 study suggest that BLV 10 mg has better antiviral efficacy than 2 or 5 mg doses when used in the absence of pegIFNα; good clinical results were also reported in three anecdotal cases of CHD while on therapy with BLV 10 mg (25). However, the lower dose of 2 mg appeared to be superior in MYR 203 study where BLV was used in combination with pegIFNα. The reasons why BLV 10 mg was inferior to BLV 2 mg when used in combination with pegIFNα are unclear. Thus, while it has been proposed that subcutaneous injections of 10 mg BLV monotherapy daily may be used for long-term treatment of CHD, further studies are needed to establish the long-term safety (bile acid increase, in particular in patients with cirrhosis) and acceptability (daily injections) as well as efficacy (maintained suppression/undetectable HDV RNA, normal ALT, and HBsAg loss) of this approach. Despite the known side effects of pegIFNα, combination of 2 mg BLV and pegIFNα had the best response and deserves further studies. In addition, the possibility of combining BLV with pegIFNλ, which has less side effects should also be evaluated. One finding in support of BLV monotherapy is that many patients normalized ALT during therapy despite persistent HDV viremia. In the MYR 203 trial, 11 patients receiving 2 mg BLV monotherapy normalized ALT though 9 of them still had detectable HDV RNA at the end of therapy, and 3 patients maintained normal ALT at the end of follow-up.

Ongoing studies might shed more light on optimal regimen of BLV and its efficacy as monotherapy or in combination with pegIFNα. One study (MYR 204) is evaluating 48 week treatment of combination of 2 or 10 mg of BLV with pegIFNα, compared to pegIFNα alone, and 144-week of BLV 10 mg monotherapy. Another study is a phase 3 study (MYR 301) evaluating 2 *vs.* 10 mg BLV monotherapy for 144 weeks vs. 10 mg BLV monotherapy for 96 weeks. The primary outcome of MYR 301 study is a combined response of undetectable HDV RNA or ≥2 Log decrease in HDV RNA plus ALT normalization at 48 weeks (ClinicalTrials.gov accession number NCT03852719).

Although the phase 3 trials are still ongoing, the European Medicines Agency has afforded a conditional marketing authorization to BLV on July 31, 2020 under the trade name Hepcludex (26). The recommended dose was 2 mg even though this dose of BLV when used as monotherapy was inferior to 10 mg. The optimal treatment duration was stated as unknown and the recommendation was to continue treatment as long as it is associated with clinical benefit though it did not specify how clinical benefit should be measured and the product information

acknowledged the lack of data on long-term impact (>48 weeks) of bile salt increase induced by BLV. CHD is designated a rare disease by both US FDA and the European Medicines Agency allowing treatment for CHD to be approved under the Orphan Drug Act; however, this is not equivalent to authorization of a drug while phase 3 trials are ongoing.

Future treatments

Two therapeutic approaches can be envisioned. Similar to HBV functional cure, one being finite therapy with a combination of BLV or LNF (with ritonavir) and pegIFNα or pegIFNλ with the goal of undetectable HDV RNA and HBsAg loss off treatment in a high percent of patients; the other is simple and safe long-term maintenance therapy similar to nucleos(t)ide analogue for HBV, based on BLV or LNF (with ritonavir) monotherapy, with the goal of keeping HDV RNA undetectable or suppressed in the presence of the HBsAg. Different levels of virologic responses should be separately reported in clinical trials and correlated with biochemical and clinical responses to help identify a virologic threshold that correlates with inactive HDV carrier state. It will be also important to assess therapy efficacy in terms of histological endpoints by performing sequential liver biopsies.

Given the central role of HBsAg in HDV infection, in addition to drugs directly targeting HDV lifecycle, clinical trials evaluating the combination of these direct-acting antivirals and drugs that specifically inhibit production of HBsAg, notably interfering RNAs and antisense oligonucleotides that have demonstrated safety and efficacy in decreasing HBsAg levels in patients with chronic hepatitis B (27), should be evaluated.

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Legend to Figure 1

HDV life cycle and sites of action of different antivirals

The HDV enters into the hepatocytes through the Sodium Taurocholate Co-transporting Polypeptide (NTCP), which is a functional membrane receptor for the HDV. Bulevirtide docks to the NTCP, blocking the entry of the HDV into hepatocytes. Within the hepatocyte HDV discards the HBsAg coat and migrates to the nucleus. In the nucleus, the viral RNA is replicated by the RNA-polymerases of the host, with the participation of the HDV ribozyme. The HDV ribonucleoprotein migrates to the cytoplasm where it is coated with the HBsAg to assemble into the virion. For HDV-RNA to combine with the HBsAg, it is necessary that the large HDAg of the HDV is farnesylated by a cytoplasmic farnesyl-transferase. The farnesyl-transferase inhibitor Lonafarnib interferes with the farnesylation process, preventing the assembly of the virion. Mature HDV virions are released from the hepatocyte via the trans-Golgi network; the HBsAg secretion inhibitor Nucleic Acid Polymer REP-2139 blocks the assembly/release of subviral HBsAg particles reducing available HBsAg for HDV morphogenesis and export (adapted from reference 28).

Table 1. Virologic Responses to Ritonavir-boosted Lonafarnib Treatment with or without pegIFNα or pegIFNλ

Study	*Treatment arms*	*Rx Duration (weeks)*	*N*	*EOT HDV RNA ≥2 log decline / BLQ**	*24 Weeks Post-Rx HDV RNA BLQ* / undetectable*	*HBsAg loss*
LOWR-2[17]	LNF 25 mg bid + RTV 100 mg bid	24	6	1 / 0	NR	NR
	LNF 50 mg bid + RTV 100 mg bid	24	13	6 / 5		
	LNF 25 mg bid + RTV 100 mg bid + pegIFNα2a 180 μg qw	24	5	3 / 3		
	LNF 50 mg bid + RTV 100 mg bid + pegIFNα2a 180 μg qw	24	4	4 / 2		
LOWR-3[18]	LNF 50 or 75 or 100 mg qd + RTV 100 mg qd	12 or 24	21	6 / 4 **	NR	NR
LOWR-4[19]	Starting dose LNF 50 mg bid	24	15	4 / 1	3 / 0	NR

	+ RTV 100 mg bid, escalating every 2-4 weeks to LNF 75 mg bid + RTV 100 mg bid followed by LNF 100 mg bid + RTV 100 mg bid					
LIFT HDV[20]	LNF 50 mg bid + RTV 100 mg bid + pegIFNλ 180 μg qw	24	26	25 / 11	NR / 5	0
LIMT HDV[21]	pegIFNλ 120 μg qw pegIFNλ 180 μg qw	48	19 14	4 / 3 7 / 5	2 / 3 5 / 5	NR

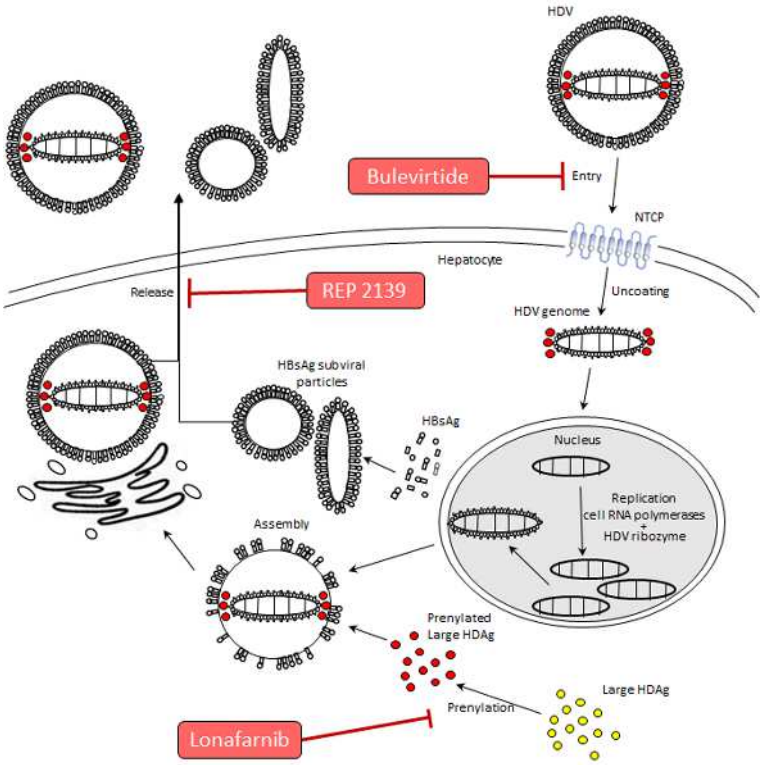
BLQ: below the limit of quantification, LNF: lonafarnib, pegIFNα2a: pegylated interferon alfa-2a, pegIFNλ: pegylated interferon lambda, RTV: ritonavir; NR: not reported. *The quantitative HDV RNA assays used in the above trials had a lower limit of quantification of 40 IU/mL (LIFT HDV) or 14 IU/mL (LOWR-2, LOWR-3, LOWR-4 and LIMT HDV); **Aggregate data from all six treatment arms

Table 2. Virologic Responses to Bulevirtide Treatment with or without pegIFNα2a and Tenofovir disoproxil fumarate

Study	*Treatment arms*	*N*	*End of treatment HDV RNA**	*Post-treatment HDV RNA**	*HBsAg response*
MYR 202[22]			≥2 log decrease or undetectable after 24 wks of BLV	≥2 log decrease or undetectable 24 wks after end of BLV	HBsAg loss 24 wks after end of BLV
	TDF 12 wks *then* BLV 2 mg + TDF 24 wks *then* TDF 24 wks	28	13	2	1
	TDF 12 wks *then* BLV 5 mg + TDF 24 wks *then* TDF 24 wks	32	15	3	2
	TDF 12 wks *then* BLV 10 mg + TDF 24 wks *then* TDF 24 wks	30	23	3	0
	TDF 60 wks	30	1	0	0
MYR 203[23,24]	48 wks treatment in all arms		Undetectable at EOT	≥2 log decrease / undetectable at	≥1 log decrease / negative at 24

				24 wks post-EOT	wks post-EOT
	pegIFNα2a 180 μg	15	2	0 / 0	0 / 0
	BLV 2 mg + pegIFNα2a 180 μg	15	9	3 / 8	6 / 4
	BLV 5 mg + pegIFNα2a 180 μg	15	6	3 / 4	2 / 0
	BLV 10 mg + pegIFNα2a 180 μg	15	13	4 / 1	1 / 1
	BLV 2 mg	15	2	4 / 1	0 / 0
	TDF + BLV 5 mg bid	15	6	2 / 5	0 / 0

BLV: bulevirtide, pegIFNα2a: pegylated interferon alfa-2a, TDF: tenofovir disoproxil fumarate, NR, not reported. *For all trials, the lower limit of quantification of HDV RNA assay was 14 IU/mL.



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