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Review Article

NOVEL ENTRY INHIBITORS FOR VIRAL HEPATITIS D TREATMENT: BULEVIRTIDE

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ABSTRACT

Chronic hepatitis D virus infection is the most severe form of viral hepatitis. Hepatitis delta virus (HDV) is a faulty RNA virus that needs hepatitis B virus surface antigen (HBsAg) for the completion of its life cycle. Hepatitis B virus (HBV) receptor, sodium taurocholate cotransporting polypeptide (NTCP), is used by HDV to infect hepatocytes. The replication of the HDV genome, which is a circular single-stranded RNA and encodes for a single HDAg that occurs in two forms (S-HDAg and L-HDAg), is carried out by the host RNA polymerases. Antiviral therapy is urgently needed to protect patients from hepatocellular carcinoma or end-stage liver disease and poses an important public health issue in many countries. There is still a need for efficient pharmacological therapies for chronic hepatitis D (CHD). A good strategy to stop new infections is to stop virus from entering cells. A new virion entry inhibitor called bulevirtide is now a promising treatment for both infections because it prevents the virion from entering the hepatocyte through the hepatic sodium/taurocholate cotransporting polypeptide Before bulevirtide's conditional approval by the EMA (European Medicines Agency) in July 2020 for the treatment of chronic HDV infection in adult patients with compensated liver disease, therapy options were restricted to the off-label use of pegylated interferon alfa. (NTCP) receptor. We will outline the most recent discoveries about the HDV life cycle that have prompted the development of noveldrug bulevirtide.

Keywords: HDV, HBV, Bulevirtide, Entry inhibitor, Compensated cirrhosis

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INTRODUCTION

Hepatitis Delta virus (HDV) is a single-stranded RNA virusoid that relies on the hepatitis B virus (HBV) for replication and encapsulation, sustains chronic hepatitis delta (CHD). HDV also known as RNA satellite virus affects roughly 12-72 million people globally. When HBV and HDV are co-infected, people with CHD have a much higher chance of developing cirrhosis and hepatocellular cancer than those with HBV mono-infection [1]. Cirrhosis, hepatocellular cancer, and liver transplantation are the most common outcomes of chronic viral hepatitis globally. The main culprits are the B, C, and D viruses. Over 290 million people worldwide have chronic HBV infection. According to current estimates, 58 million people worldwide have chronic HCV infection. Infection with the chronic form of the HDV affects between 12 and 60 million people worldwide [2]. HDV has been characterised as the most severe form of viral hepatitis after chronicity has been established, progressing to cirrhosis in 10%–15% of patients within 2 y and in 70%–80% of patients within 5–10 y [3-5]. Despite this, there are currently insufficient HDV therapeutic alternatives available. Pegylated-interferon (peg-INF) is recommended by current international standards, although its reported sustained virological response (SVR) rates are only 20% to 30% lower than those of other treatments [1]. There are significant geographic variations, with the highest prevalence rates reported in the nations of Mongolia, Pakistan, Moldova, and Western and Middle Africa [3, 4]. In this review, we will focus on HDV virology and its life cycle, previous therapeutic modalities and the most recent treatment options with special consideration on new drugBulevirtide.

Structure and life cycle of HDV

The HDV virion is a tiny RNA virus (36 nm in diameter) with an inner nucleocapsid that consists of a short (~1.7-kb) single-stranded, circular RNA and approximately 200 molecules of hepatitis D antigen (HDAg). The HDV genome is the smallest of all mammalian viruses and resembles viroids structurally. It produces the HDAg protein, which are of two different sizes: small HDAg (S-HDAg) and large HDAg (L-HDAg). The two versions are structurally similar with the exception of the L-19 HDAg's extra amino acids at the C-terminus. The HDV virion's exterior coat is made up of HBV-derived components, necessitating co-infection with HBV and its small, medium, and large HBsAg. The HDV genome and HDV antigen isoforms are encased in a lipid envelope, which contains the isoforms of HBsAg. The big HBsAg is subsequently myristoylated at the N-terminus to get it ready for cell entrance [1]. All three types of hepatitis B surface antigen (HBsAg) proteins produced from HBV are contained within the lipid envelope that surrounds this inner nucleocapsid. HDV is unable to infect human without HBsAg [5]. The pre-S1 domain of the big HBsAg must bind to the sodium-taurocholate co-transporting polypeptide (NTCP), a bile acid transporter expressed on the basolateral plasma membrane of human hepatocytes, for the HDV viral life cycle to begin when HBV and HDV reach the hepatocytes. It is believed that a number of single nucleotide polymorphisms (SNPs) in the NTCP coding gene, SLC10A1, affect the binding ability of HBsAg to NTCP. This governs the susceptibility of hepatocytes to HBV and HDV infection. [6]The HDV genome is transported to the nucleus by HDAg-mediated interactions during cell entry and uncoating, where it uses host RNA polymerase II for genome replication. There are no DNA archiving events or intermediates. Instead, HDV replication occurs in double rolling circle mechanism, driven by the catalytic activity of RNA polymerase II, SHDAg, and an incoming circular negative strand template genome, to produce linear multimeric copies of antigenomic RNA. The precise cleavage of these linear multimeric copies then occurs at a single ribozyme site that is encoded once in each antigenome. The resulting linear antigenomic monomers are then linked together to form antigenomic circles, which act as a template for the synthesis of linear multimers of genomic RNA with opposite polarity. Through autocatalytic cleavage at a different ribozyme site encoded once in each genomic RNA, these in turn self-process into linear genomic monomers. The genomic monomers are joined together to form rings that can either sustain more replication cycles or contain developing virions [1, 5, 7, 8]. A smaller antigenomic sense mRNA is also transcribed off of the genomic template. This mRNA codes for the two different forms of HDAg. S-HDAg is carried into the nucleus, where it helps in HDV replication. Prior to assembly, L-HDAg passes through prenylation, which prevents HDV replication in the nucleus. New HDAg molecules join

with fresh genomic RNA transcripts to create RNPs that are exported to the cytoplasm. Hepatitis B virus (HBV) envelop proteins connect with new HDV RNPs, which are then formed into HDV virions. The finished HDV virion is then ready to be released into the trans-golgi network and infect fresh hepatocytes. After infection, HDV infection causes hepatocyte damage by direct cytopathic effect or via still incompletely understood immune-mediated mechanism [5, 8].

Problems with chronic delta hepatitis treatment

Due to viral hepatitis andits rapid progression to liver cirrhosis and hepatocellular carcinoma (HCC), the main objectives of therapy are to lessen the occurrence of severe outcomes, the requirement for liver transplantation, and, ultimately, the patient's mortality from liver-related issues. Normalization of transaminases, elimination of circulating HDV RNA, and HBsAg seroconversion are the intermediate surrogate objectives. Unfortunately, treating Delta hepatitis is difficult due to the following factors, firstly, patients frequently have advanced liver disease that is difficult to treat. Transaminase flares frequently occur during treatment or after treatment withdrawal and suppression of HDV replication may be linked to HBV flares. A lack of standardisation in testing and response criteria. Common association with autoimmune liver disease that may make it difficult to use interferon or other immunomodulating medications. Lastly, the lack of convenient/effecient HDV infection models has hampered the development of effective therapeutics. These difficulties are partially brought on by the lack of new therapeutic options and the subpar outcomes of the present medications, which are characterised by low response rates and low efficacy. A>2 log decrease in blood HDV RNA levels in conjunction with ALT normalisation has been accepted as a measure of initial treatment success in clinical studies. This is due to the uncertainty surrounding the long-term beneficial effects of HDV suppression and the challenges in achieving HBsAg clearance. These therapeutic intermediate and surrogate endpoints have made it possible in recent years to examine the effectiveness of novel investigational medications in treating HDV infection and HDV-related hepatitis [10].

Over the past few years, various strategies have been tested to prevent and reduce HDV replication. The three important treatment mechanisms are: (1) inhibition of HDV prenylation; (2) inhibition of HBsAg release; and (3) inhibition of cell entry. Nucleos(t)ide analogues, such as tenofovir disoproxil fumarate (TDF), can effectively cure chronic hepatitis B, however, they are ineffective for treating chronic liver disease (CHD). In one out of every four CHD patients, pegylated interferon alpha (PEG-IFN), when administered for 48 w, may result in a durable virologic response. PEG-IFN, however, has significant side effects and should not be used in people with liver cirrhosis. Therefore, patients with CHD require therapeutic alternatives that are both efficient and secure. Clinical trials are being conducted to test various antiviral drugs [11]. Oral lonafarnib therapy for chronic HDV markedly decreased virus levels, and the fall in viral replication strongly corresponded with serum drug concentrations. The drug was administered in a dose of 200 mg taken twice daily. Unfortunately, there were substantial side effects that were increased by this dosage. Due to this, additional studies were conducted with lonafarnib 100 mg twice daily, either alone or in combination with pegylated interferon and ritonavir. Although both treatments were linked to a>2 log reduction in HDV viremia, a sizable portion of patients continued to have negative side effects [12]. Broad-spectrum antiviral drugs known as nucleic acid polymers (NAPs) are effective against hepatitis B virus (HBV) infection because they can prevent the release of the virus' surface antigen (HBsAg). This pharmaceutical action prevents the circulation from replenishing with HBsAg, enabling host-mediated clearance. A nucleic acid polymer called REP 2139 has been demonstrated to remove HBsAg by preventing the release of subviral particles. In an uncontrolled phase 2 study, this medication was assessed for the treatment of HDV infection [13].

In the absence of adequate treatment options, the first-in-class entry inhibitor of HBV and HDV, bulevirtide, has recently been approved EU for chronic HDV infection in plasma (or serum) HDV RNA-positive adult patients with compensated liver disease. The continuation of clinical trials to verify efficacy and safety for chronic hepatitis D was part of the accelerated conditional approval as a priority drug [14]. It is a synthetic lipopeptide made up of 47 amino acids from the HBV large surface protein's preS1 domain. The sodium taurocholate co-transporting polypeptide (NTCP), a bile salt liver transporter that enables the entry of HDV and HBV into hepatocytes, binds to it and competitively inhibits it. The removal of infected hepatocytes from the liver may result from this inhibition, which mayhelps in hepatocyte regeneration and prevent HDV/HBV reinfection in healthy hepatocytes [15, 16].

Pre-clinical studies

Bulevirtide capacity to prevent the spread of HBV after infection was studied by Volvz. *et al.* HBV was transmitted to Urokinase-type plasminogen activator/severe combined immunodeficiency (uPA/SCID) mice that had been reconstituted with human hepatocytes. Daily subcutaneous bulevirtide infusions were started for three days, three weeks, or eight weeks after HBV vaccination. Immunohistochemistry was used to measure the viral loads in the liver and serum and to visualise them. The fact that viremia, antigen levels, and the number of HBcAg-positive human hepatocytes were not increased six weeks after treatment showed that drug effectively stopped viral spreading from the initially infected human hepatocytes. In animals exhibiting modest levels of circulating virions, the drug effectively inhibited HBV dissemination even when treatment was initiated during the ramp-up phase of infection. It is noteworthy that during 6 w of treatment, both the quantity of HBcAg-positive hepatocytes and intrahepatic covalently closed circular DNA (cccDNA) burdens remained in line with those observed in mice euthanized 3 w after infection. Drug administration had no impact on the human hepatocyte half-life or changed virion productivity in any of the experimental scenarios [18].

Engelke *et al.* conducted their study to get an insights into the early infection events of the HBV and HDV. This knowledge is limited because of the lack of a cell culture system supporting the full replication cycle for these important pathogens. They used the human hepatoma cell line HepaRGfor experiment as it allows the experimental induction of a differentiated state, thereby gaining susceptibility toward HBV and HDV infection. In their previous study they identified HBV envelope protein-derived lipopeptides. This comprises of amino acids 2 though 48 of the preS-domain of the L-surface protein, which block infection already at picomolar concentrations. To map the responsible sequence for the peptides' activity, they used an Escherichia coli expression system that allowsmyristoylation and investigated recombinant HBVpreS-GST fusion proteins with deletion-and point-mutations for their ability to prevent HBV and HDV infection. They concluded that firstly, a myristoylated HBVpreS/2-48-GST fusion protein efficiently interferes with HBV infection of HepaRG cells. Deletions and point mutations in the highly conserved preS1 sequence between amino acids 11 through 21 result in the loss of infection inhibition activity. Hepatitis B viruses carrying single amino acid exchanges within this region lose infectivity. Lastly, HDV infection of HepaRG cells can be inhibited by myristoylatedHBVpreS peptides with the same specificity. They concluded that HBV and HDV use at least one common step to enter hepatocytes and require a highly conserved preS1-sequence within the L-protein. This step is exceptionally sensitive toward inactivation by acylated HBVpreS1 peptides, which therefore represent a novel group of entry inhibitors that could be used for the treatment of hepatitis B and D [19].

Lütgehetmann *et al.* in their study used humanised uPA/SCID mice that were naive and chronically infected with the HBV to create a small animal model of HBV/HDV coinfection and superinfection. The GMP form of the myristoylatedpreS-peptide (bulevirtide), a lipopeptide generated from the pre-S1 domain of the HBV envelope, was used to stop de novo HBV/HDV coinfection *in vivo* for preclinical antiviral drug evaluation. Real-time polymerase chain reaction (PCR) as well as immunohistochemistry, were used to determine virological parameters at the serological and intrahepatic levels. Both HBV-infected and naive chimeric mice were successfully infected with HDV. HDV superinfection resulted in a median 0.6log

decrease in HBV viremia, which even though it was not statistically significant, raises the possibility that HDV may prevent HBV replication. The majority of human hepatocytes stained HDAg-positive in the context of HBV/HDV simultaneous infection long before HBV spreading had finished. This shows that HDV can replicate intrahepatically even in the absence of HBV infection. Additionally, compared to animals with HBV mono-infection, the increase in HBV viremia and intrahepatic cccDNA burdens was noticeably slower. The occurance of HDV infection *in vivo* was effectively prevented by treatment with the HBV entry inhibitor bulevirtide [20].

Pharmacokinetics

Bulevirtide followed non-linear pharmacokinetics in healthy volunteers, following a two-compartment target-mediated drug disposition model. Aftersubcutaneous (SC) and intravenous (IV) doses, bulevirtide exposure increased disproportionately with increasing dose; clearance and volume of distribution decreased. The bioavailability after SC dosing was calculated to be 85%. After the first few weeks of bulevirtide 2 mg dosing, steady state is anticipated with 2-fold accumulation ratios for the maximum drug concentration (Cmax) and area under the curve (AUC). Time to Cmax (tmax) ranged from 0.8 to 10 mg for bulevirtide. Excretion is by a first-order process and it mainly involve target binding to NTCP with elimination half-life (t1/2) is 4–7 h. More than 99% of bulevirtide is bound to plasma proteins *in vitro*, therefore active metabolites are not anticipated [21].

Clinical studies

In one of the pilot study (phase Ib/IIa) Bogomolov *et al.*, reported the interim results of a their trial on chronically infected HDV patients. In their study 24 patients with CHD infection were equally randomized (1:1:1) to receive myrcludex B, or PegIFNα-2a or their combination. Patients were evaluated for virological and biochemical response and tolerability were assessed at weeks 12 and 24. Although there were no significant differences in HBsAg levels, the combination arm showed a markedly stronger antiviral effect. There was a drop in HDV-RNA of >1log and five of seven patients developing HDV-RNA negativity. The most common adverse event, which was typically brief and asymptomatic, was an elevation in total bile acid because bulevirtide binds to the same receptor of bile salt transporter [22].

In an open-label phase 2b clinical trial conducted by Wedemeyer *et al.*,120 individuals were divided into four groups and randomly assigned to receive either tenofovir alone or bulevirtide 2, 5, or 10 mg for 24w followed by a 24w period continuing TDF. Bulevirtide showed a dose-dependent antiviral efficacy against HDV. This was also associated with improvements of biochemical activity and liver stiffness. The drug was well tolerated and apart from bileacids increase, no specific adverse event was reported [23].

In one of the Phase 2 trial (MYR203 trial) conducted by Wedemeyer *et al.*, in this study 60 HBeAg negative patients with chronic HBV/HDV co-infection were randomized in 4 arms. Patients received 180 µg PEG-IFNα once weekly or bulevirtides. c. at 2 mg or 5 mg once daily plus PEG-IFNα, or bulevirtide alone for 48wks. Treatment-free follow-up was 24wks. Administration of bulevirtide for 48wks alone and in combination with PEG-IFNα was found to be safe. Combination therapy produced HDV RNA decline and induced profound HBsAg declines in a substantial number of patients. This study provides first evidence that entry inhibition by bulevirtide in combination with PEG-IFNα have curative potential for chronic HDV and HBV infection [24].

24 patients were enrolled in the first phase IIa study and randomly assigned to receive (I) bulevirtide 2 mg (daily) alone for 24 w, followed by PEG-IFN 180 g (weekly) for 48 w, (II) bulevirtide 2 mg (daily) and PEG-IFN 180 g (weekly) combined for 24 w, (III) PEG-IFN alone for 24 w, or (IV) bulevirt At week 24, HDV RNA dramatically decreased in all treatment groups. All patients who received bulevirtide monotherapy saw a drop in HDV RNA levels, and at week 24, two patients developed HDV RNA negative status. As five patients in treatment group II had negative HDV RNA at week 24, it is interesting to note that the addition of PEG-IFN boosted the number of patients who were HDV RNA negative. Additionally, the combination group showed a more dramatic quantitative HDV RNA reduction. At treatment week 12, none of the patients met the primary goal of>0.5 log decrease of HBsAg [25].

Toni Herta *et al.*, conducted their study to assess efficacy and safety of Tenofovir Disoproxil Fumarate and Bulevirtide in Chronic Hepatitis B and D Co-Infection in Real-World Patients. They examined the course of treatment for patients with chronic hepatitis delta using BLV (2 mg/day) and tenofovir disoproxil fumarate (TDF) (245 mg/day) (CHD). After 24 w, treatment responses were determined virologically (2 log reduction in HDV RNA or suppression of HDV RNA below the lower limit of detection) and biochemically (normalisation of serum ALT). There were seven patients enlisted (four with liver cirrhosis Child-Pugh A). Five of the seven patients with elevated baseline serum ALT showed a virologic response after 24 w, and three of the six patients with elevated baseline serum ALT showed a biochemical response. Three instances had extended treatment data>48 w available; two of them showed ongoing virologic and biochemical responses, while the third showed an HDV-RNA breakthrough. There were no adverse effects noted [26].

In another IIb study (MYR204 trial), 175 patients with compensated CHD were randomised to 4 arms. The different treatment arms were 180 lg/week of pegIFNa monotherapy for 48 w with a post-treatment follow-up of 48 w; 180 lg/week of pegIFNa plus 2 mg/day bulevirtide for 48 w, followed by 48 w of BLV 2 mg monotherapy; 180 lg/week of pegIFNa plus 10 mg/day BLV for 48 w, followed by 48 w of BLV 10 mg/day monotherapy and BLV 10 mg/day monotherapy for 96 w with a post-treatment follow-up of 48 w for the 3 last arms. Combination therapy and bulevirtide 10 mg monotherapy resulted in high rates of HDV RNA decline while drug alone resulted in the highest rate of ALT normalisation. More than 1 log IU/ml decline of HBsAg levels vs. baseline was achieved only in the combination group (12% with BLV 2 mg and 8% with BLV 10 mg) and in the pegIFNa monotherapy group (4%) [27].

In one of the longest Phase 3 clinical trial (MYR301 trail) which was multicenter, open-label, randomized Clinical Study to assess efficacy and safety of bulevirtide in Patients with Chronic Hepatitis Delta at 240 wks. 150 patients with chronic HBV/HDV coinfection were randomised to 3 different groups. Control group (48 w no treatment followed by 96 w 10 mg BLV), second group, 2 mg bulevirtide (144 w of 2 mg BLV followed by 96 w of off-treatment follow-up) and third group, 10 mg bulevirtide (144 w of 10 mg BLV followed by 96 w of offtreatment follow-up). At week 24, 4%, 55%, and 68% of the patients had virological responses (a reduction in HDV RNA of>2 log IU/ml), however only 0%, 6%, and 8% had undetectable HDV RNA, or 6 IU/ml. In the three groups, HDV RNA levels decreased by 0.079, 2.2, and 2.4 log IU/ml, respectively. The rates of ALT normalisation rose from 6% in the control group to 53% and 38% in the groups receiving the active drugs (6% vs. 53%, p 0.0001; 6 vs. 38%, p 0001). In comparison to the control group, the equivalent frequencies of combined responses were 0%, 37%, and 28% (p 0.001). Therefore, HDV RNA levels significantly decreased and biochemical disease activity improved after 24 w of treatment with BLV 2 or 10 mg, but no apparent dosage impact was seen in this trial. The HBsAg levels were unaffected by bulevirtide monotherapy, same like in the MYR202 study. Patients with chronic HDV infection responded well to bulevirtide monotherapy, with few serious adverse effects (AEs) and the majority of AEs being mild-to-moderate in severity. Patient-reported outcomes (Hepatitis Quality of Life Questionnaire [HQLQTM], including SF-36 and 15 supplementary items) were also assessed in this study From baseline to week 24, BLV 2 mg-treated patients reported improvements in all domains on the HQLQTM, notably>5-point improvements in general health, bodily pain, vitality, mental health, hepatitis specific (HS) limitations, and HS health distress and>4 points in social functioning and role functioning of emotional domains [28]. The important clinical studies are summarised in the table 1.

Table 1: Summary of the clinical studies on Bulevirtide

S. No.	Patients/Groups	Authors	Status	Results
1	• 24 patients with CHD infection • Randomized (1:1:1) to receive myrcludex B, or PegIFNα-2a or their combination • Evaluation at weeks 12 and 24	Bogomolov *et al.* [22]	Phase Ib/IIa	• Strong effect on HDV RNA serum levels and induced ALT normalization under monotherapy.
2	• 120 individuals • Randomly assigned to receive either tenofovir alone or Bulevirtide 2 mg, 5 mg or 10 mg • For 24weeks and followed by another 24weeks period.	Wedemeyer *et al.* [23]	Phase 2b	• Dose-dependent antiviral efficacy against HDV associated with improvements of biochemical activity and liver stiffness
3	• 60 HBeAg negative patients with chronic HBV/HDV co-infection • Randomized in 4 arms,180 µg PEG-IFNα once weekly or bulevirtides. c. at 2 mg or 5 mg once daily plus PEG-IFNα, or bulevirtide alone for 48wks.	Wedemeyer et. al [24]	Phase 2 trial (MYR-203 trial)	• Administration of Bulevirtide for 48weeks alone and in combination with PEG-IFNα was found to be safe. • Combination therapy produced HDV RNA decline and induced profound HBsAg declines in a substantial number of patients.
4	• 24 patients • Randomly assigned to receive (I) bulevirtide 2 mg (daily) alone for 24 w, followed by PEG-IFN 180 g (weekly) for 48 w, (II) bulevirtide 2 mg (daily) and PEG-IFN 180 g (weekly) combined for 24 w, (III) PEG-IFN alone for 24 w, or (IV) bulevirtide.	Bogomolov P *et al.* [25]	Phase IIa	• Bulevirtide monotherapy results in drop in HDV RNA levels • At treatment week 12, none of the patients met the primary goal of>0.5 log decrease of HBsAg
5	• 7 patients • Treatment arm-bulevirtide (2 mg/day) plus tenofovir disoproxil fumarate (TDF) (245 mg/day)	Herta T *et al.* [26]		The first real-life data of the approved dosage of 2 mg of BLV in combination with TDF confirm the safety, tolerability, and efficacy of the registrational trial MYR-202 for a treatment period of 24 w and beyond.
6	• 175 patients • Randomised to four arms, 180 lg/week of pegIFNα monotherapy for 48 w with a post-treatment follow-up of 48 w; 180 lg/week of pegIFNα plus 2 mg/day bulevirtide for 48 w, followed by 48 w of bulevirtide 2 mg monotherapy; 180 lg/week of pegIFNα plus 10 mg/day BLV for 48 w, followed by 48 w of BLV 10 mg/day monotherapy and bulevirtide 10 mg/day monotherapy for 96 w with a post-treatment follow-up of 48 w for the 3 last arms	Asselah A *et al.* [27]	Phase IIb (MYR-204 trial)	Combination therapy and bulevirtide 10 mg monotherapy resulted in high rates of HDV RNA decline while drug alone resulted in the highest rate of ALT normalisation.
7	• 150 patients with chronic HBV/HDV coinfection • Randomised to 3 different groups. Control group (48 w no treatment followed by 96 w 10 mg BLV), second group, 2 mg bulevirtide (144 w of 2 mg BLV followed by 96 w ofoff-treatment follow-up) and third group, 10 mg bulevirtide (144 w of 10 mg followed by 96 w of off treatment follow-up).	Gilead press release [28]	• Phase III clinical trial (MYR-301 trail) • Multicenter, open-label, randomized clinical study	Patients with chronic HDV infection responded well to bulevirtide monotherapy, with few serious adverse effects (AEs) with the majority of them being mild-to-moderate in severity.

CONCLUSION

Since the discovery of HDV, the first anti-HDV treatment has only been conditionally approved by the EMA and US-FDA has not yet granted approval. With the development of viral entry inhibitors, farnesylation inhibitors, viral particle formation blockers and interferon lambda, new promising treatment options are becoming available for patients with CHD. Bluvertide, the first-in-class entry inhibitor, has shown to reduce HDV replication and normalise ALT levels in a significant proportion of patients with compensated CHD, either as monotherapy or combined with pegIFNα. Overall, a favorable safety profile as well as a marked biochemical and virological response were reported by the trials. However, there are still a lot of unanswered questions regarding bulevirtide treatment. Given the relatively high costs of treatment (around 13.000 Euro per month), it is especially important to determine the ideal length of time for treatment, although there is no clear suggestion on this subject. The absence of HBsAg level reduction and HDV-RNA relapse upon treatment cessation indicate the need for additional research concentrating on the ideal treatment schedule while also indicating that bulevirtide probably needs to be administered lifelong. To assess the effect of bulevirtide medication on clinical outcomes in hepatitis delta patients, further long-term data (studies) are required.

ETHIC STATEMENT

Not applicable

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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