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Bulevirtide for chronic hepatitis delta: from clinical trials to real life data: an expert opinion report

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ABSTRACT

Hepatitis D virus (HDV) is a small RNA virus that requires Hepatitis B Surface Antigen (HBsAg) for its envelope. Eight genotypes with more than 80 % sequence homology and many subgenotypes have been described. Worldwide prevalence of chronic hepatitis delta (CHD) is estimated at about 5 % of chronic hepatitis B cases, translating to 15–20 million individuals. The diagnosis of HDV infection involves presence of antibodies to hepatitis D antigen (anti-HDV antibodies). *Anti-HDV total antibody indicates HDV exposure (not infection). To document infection; the patient needs to undergo PCR testing and only if PCR is positive should the diagnosis of HDV ongoing infection done.* Testing for the antibodies should be performed in all HBsAg-positive persons. CHD is more severe and progressive than HBV mono-infection, with a higher risk of cirrhosis and hepatocellular carcinoma (HCC), *transplantation and death*. Pegylated interferon-alpha (pegIFN-a) has been used for treating CHD with only limited durable responses. A 48-week course of weekly subcutaneous injections of pegIFN-a suppresses HDV replication in approximately 20–30 % of patients 24 weeks off therapy, with significant side effects. Bulevirtide (BLV) was approved by the European Medicines Agency (EMA) in 2020 for CHD and compensated liver disease. Since its approval, real-life data on the use of BLV have been accumulating, with most treated patients in Europe having advanced fibrosis or cirrhosis. Real life data efficacy is concordant to that seen in clinical trials, with many patients achieving significant reductions in HDV RNA levels and ALT normalization after several months of treatment, and favorable safety. However, HBsAg loss is relatively rare. Finite therapy of BLV, in combination with pegIFN-a, leads to significant durable response, with more than 30 % of patients achieving HDV RNA undetectability off therapy. We need new finite therapies. Further real-world data and newer therapies are required for this severe disease.

1. Introduction: What is Hepatitis D virus?

Hepatitis D virus (HDV) is an opportunistic virus that only affects individuals who are already infected with HBV. HDV is a small RNA virus that requires Hepatitis B Surface Antigen (HBsAg) for its envelope (Fig. 1), for entry into hepatocytes and secretion (Asselah et al., 2023). The entry receptor for Hepatitis B Virus (HBV) (and therefore HDV) has been identified to be the sodium taurocholate cotransporting polypeptide (NTCP) (Yan et al., 2012). A strong knowledge of the virology and immunology of HDV infection is mandatory for drug development (Khalfi et al., 2023-Usai et al., 2022, Zhang and Urban, 2020). HDV belongs to the genus deltavirus within the family of Kolmioviridae. Eight genotypes with more than 80 % sequence homology and many subgenotypes have been described (Le Gal et al., 2017). Genotype 1 is the most prevalent worldwide. The genome is a circular, single-stranded RNA of approximately 1700 nucleotides. Entry into hepatocytes of HDV occurs through the binding of large HBsAg in the HDV coat to the NTCP. The HDV RNA is complexed with the HDAg (small and large) forming a ribonucleoprotein complex. This complex acquires the HBV envelope for viral release and propagation.

2. Diagnosis

The diagnosis of HDV infection involves presence of antibodies to hepatitis D antigen (anti-HDV antibodies) (Fig. 2). Testing for the

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Abbreviations:

(BLV) Bulevirtide
(CHD) Chronic hepatitis D
(EASL) European Association for the Study of the Liver
(EMA) European Medicines Agency
(HCC) Hepatocellular Carcinoma
(HBV) Hepatitis B virus
(HCV) Hepatitis C virus
(HDV) Hepatitis Delta Virus
(HBsAg) Hepatitis B Surface Antigen
(pegIFN) Pegylated-Interferon
(NTCP) Sodium taurocholate cotransporting polypeptide
(RT-PCR) Reverse-transcriptase–polymerase-chain-reaction

antibodies should be performed only in HBsAg-positive persons. *A*nti-HDV total antibody indicates HDV exposure (not infection). To document infection; the patient needs to undergo PCR testing and only if PCR is positive should the diagnosis of HDV ongoing infection done. In-house and commercial reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays are available for quantification of HDV RNA with the use of amplification targets in conserved regions of HDAg or the ribozyme (Wedemeyer et al., 2025). A reliable HDV RNA quantitation assay is the base for not only diagnosis but also treatment response. People with HBV infection remains at high risk of becoming infected with HDV. We have to increase awareness, and to improve prevention.

3. Natural history

Chronic hepatitis D is more severe than chronic hepatitis B. During 1–15 years of follow-up in, histologic deterioration was documented in 77 % of Italian patients who were positive for anti-HDV antibodies, as compared with 30 % of HBsAg carriers who did not have anti-HDV antibodies (Fattovich et al., 1987). CHD is more severe and progressive than HBV mono-infection, with a higher risk of cirrhosis and hepatocellular carcinoma (HCC) indicating that in patients with cirrhosis, HDV adds an additional oncogenic factor for HCC independently of HBV (Alfaiate et al., 2020; Roulot et al., 2024b). In a study also from Italy, HDV infection, when compared to HBV mono-infection, increased the risk of hepatocellular carcinoma by a factor of 3 (Fattovich et al., 2000). It has been reported that persistent HDV viremia is the most important risk factor for progression to cirrhosis. (Roulot et al., 2020; Kamal et al., 2020). HDV chronic infection is associated with a higher risk of HCC, transplantation and death. Transient Elastography (Fibroscan – Echosens™) demonstrates good diagnostic performance for advanced fibrosis and cirrhosis in patients with CHD. Advanced fibrosis is highly probable for LSM values ≥ 10 kPa. LSM values < 6 kPa almost totally exclude significant fibrosis. Between 6 and 10 kPa, liver biopsy should be discussed (Roulot et al., 2024a).

4. What is the prevalence of HDV worldwide? Is HDV an orphan disease?

Global prevalence of hepatitis delta is estimated, with caveats, at about 5 % of chronic hepatitis B cases worldwide, translating to 15–20 million individuals globally infected (Razavi et al., 2023). CHD is highly prevalent in certain regions, especially where HBV is widespread (Sub-Saharan Africa, Southeast Asia (*Pakistan, Mongolia, etc* …), Mediterranean, and parts of South America (Amazonia)) (Polaris Observatory Collaborators, 2024). People who inject drugs and those with high-risk sexual behaviors are particularly vulnerable to both HBV and HDV due to the shared modes of transmission. Vaccination against HBV is the best preventive measure, as it also prevents HDV.

HDV is considered an orphan disease for numerous reasons, mainly due to its relatively low prevalence, lack of treatment options, and insufficient research and attention compared to more common diseases. According to the Orphan Drug Act (in the U.S.) and similar regulations worldwide, an orphan disease is defined as one that affects a small percentage of the population (typically fewer than 200,000 people in the U.S.), or a disease that lacks adequate treatment options. CHD meets these criteria due to its limited prevalence and limited treatment options.

5. Is there a role for Pegylated Interferon therapy?

Pegylated interferon-alpha (pegIFN-a) has been used for treating patients with HDV for the last 30 years, with only limited durable responses (Wedemeyer et al., 2019a,b). A 48-week course of weekly subcutaneous injections of pegIFN-a suppresses HDV replication in approximately 20–30 % of patients 24 weeks off therapy, with significant side effects. Continuous administration of pegIFNa for more than 48 weeks may lead to HBsAg loss in approximately 10 % of these patients during long-term follow up. European Association for the Study of the Liver (EASL) recommend, for patients with CHD and active replication, the use of pegIFN-a for a minimum of 48 weeks, or more if tolerability is favorable (EASL CPG., 2023). The endpoint for efficacy, in an analogous fashion to historical treatment for Hepatitis C Virus (HCV), has been defined as undetectable HDV- RNA levels at 24 weeks post-treatment. We emphasize that HDV-RNA serum levels should be regularly monitored in patients with a virological response, since relapse is common. One study reported that CHD patients treated with pegIFN-a for 48 weeks, 40 % achieved undetectable HDV-RNA levels at 24 weeks post-treatment, but only 12 % had maintained such levels after 4.5 years of follow-up (Heller et al., 2014). Therefore, the term 'sustained virological response' (used for therapy of HCV infection) should not be used

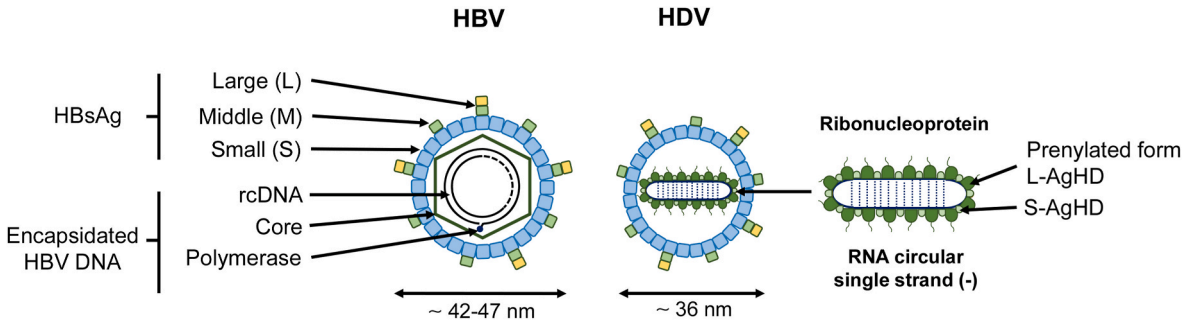

Fig. 1. Structure Hepatitis D Virus (HDV). HDV shares the hepatitis B surface antigen (HBsAg) envelope with hepatitis B virus. The virion contains a single-stranded, circular RNA genome of approximately 1700 nucleotides. HDV RNA codes for the small hepatitis D antigen (S-HDAg, 195 amino acids) required for replication. The HDV RNA is edited enabling the production of the large hepatitis D antigen (L-HDAg, 214 amino acids). L-HDAg inhibits replication of HDV and is required for viral assembly. The virions (delta particles) are approximately 35 nm in diameter. *(rcDNA: relaxed circular DNA).*

for HDV infection. We would like to inform readers that for HCV infection, if RNA is not detected 12 or 24 weeks after the end of treatment, it is a cure (HCV elimination) (Martinot-Peignoux., 2010), which is not the case for HDV (risk of relapse). In some patients negativity of treatment (we propose to define as durable virological response) may be achieved with a favorable outcome. For HDV infection, the term 'durable response' seems more appropriate (when HDV RNA remains undetectable). Therefore, it is important to follow the patients all life. A cure for HDV is achieved if there is a durable HDV RNA undetectability or if HBsAg is loss. It will be important to demonstrate clinical benefit of treatment. It is well known that pegIFN-a treatment is associated with significant side effects: flu-like symptoms (headaches, myalgias, arthralgias), pancytopenia (anemia, leukopenia, thrombocytopenia), depression and risk of suicide, and high serum aminotransferase values. This treatment is contra-indicated for patients with decompensated cirrhosis, major psychiatric illness, and autoimmune diseases. Given that long-term durable antiviral efficacy of pegIFN-a remains limited (around 10 %–20 %) and associated with poor clinical tolerability, this treatment has a limited role in CHD.

6. When treating CHD, should we use analogues for hepatitis B virus treatment?

Nucleos(t)ide analogues (for HBV reverse transcriptase inhibition) have no effect on HDV replication and therefore are not recommended (Wedemeyer et al., 2019a,b). HDV usually can reduce HBV replication. If a therapy is started to treat CHD, there is a risk of reactivations of the HBV following control of HDV. Therefore, tenofovir, entecavir or tenofovir alafenamide, have been added to HDV therapy to prevent possible reactivation of the HBV following control of HDV. When treating chronic HDV infection, it is important to add NUcs to control the HBV and avoid reactivation.

7. What is the structure and mode of action of Bulevirtide?

Bulevirtide (BLV), an N-terminally myristoylated, HBV-large-envelope-protein–derived lipopeptide, inhibits NTCP irreversibly, blocking the access of the HBsAg-coated HDV to the hepatocyte (Lempp., 2016; Hepcludex Summary of Product Characteristics, 2023). The long peptide sequence consisting of 38 amino acids, is as follows: *H-Gly-Thr-Phe--Gly-Ser-Gly-Gln-Gly-Tyr-Ser-Phe-Ser-Ile-Phe-Pro-Tyr-Ser-Gly-Ly-s-Pro-Ser-Gly-Ser-Glu-Tyr-Gly-Val-Val-Tyr-Phe-Gly-Ser-Val-Leu-Glu-Gly--Val-Phe-Ala-Pro-Phe.*

BLV has a molecular weight of approximately 4300 Da. It is designed to mimic a fragment of the preS1 region of the HBV envelope protein, which is crucial for the virus to attach to and enter human liver cells via the NTCP receptor (Lempp., 2016; Hepcludex Summary of Product Characteristics, 2023). NTCP structure displays an additional pocket formed by residues that are known to interact with preS1, presenting new opportunities for structure-based drug design (Park., 2022).

8. MYR-301 clinical trial: Bulevirtide monotherapy?

Data from a 48-week interim analysis in a phase 3, open-label, randomized trial (MYR 301)

(NCT03852719) of BLV monotherapy in patients with CHD have been reported (Wedemeyer et al., 2023). In this ongoing phase 3 trial, patients with CHD, with or without compensated cirrhosis, were randomly assigned, in a 1:1:1 ratio, to receive BLV subcutaneously at 2 mg per day (2-mg group) or 10 mg per day (10 mg group) for 144 weeks or to receive no treatment for 48 weeks followed by BLV subcutaneously at 10 mg per day for 96 weeks (control group). Patients completed 96 weeks of additional follow-up after the end of treatment. The primary end point was a combined response at week 48 of an undetectable HDV RNA level, or a level that decreased by at least 2 $\log_{10}$ IU per milliliter from baseline, and normalization of the alanine aminotransferase (ALT) level. The key secondary end point was an undetectable HDV RNA level at week 48, in a comparison between the 2 mg group and the 10 mg group. A total of 49 patients were assigned to the 2 mg group, 50 to the 10 mg group, and 51 to the control group. A primary end-point response occurred in 45 % of patients in the 2 mg group, 48 % in the 10 mg group, and 2 % in the control group ($P < 0.001$ for the comparison of each dose group with the control group) (Fig. 3). The HDV RNA level at week 48 was undetectable in 12 % of patients in the 2 mg group and in 20 % in

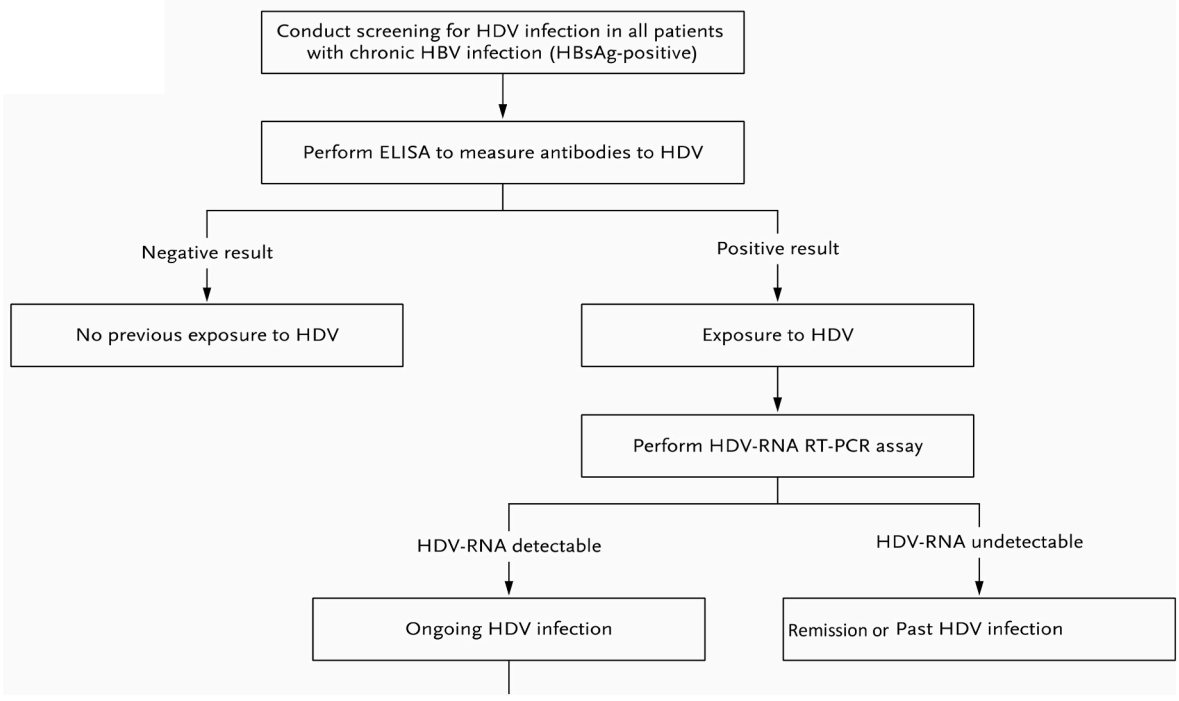

Fig. 2. Algorithm for the clinical management of HDV infection.

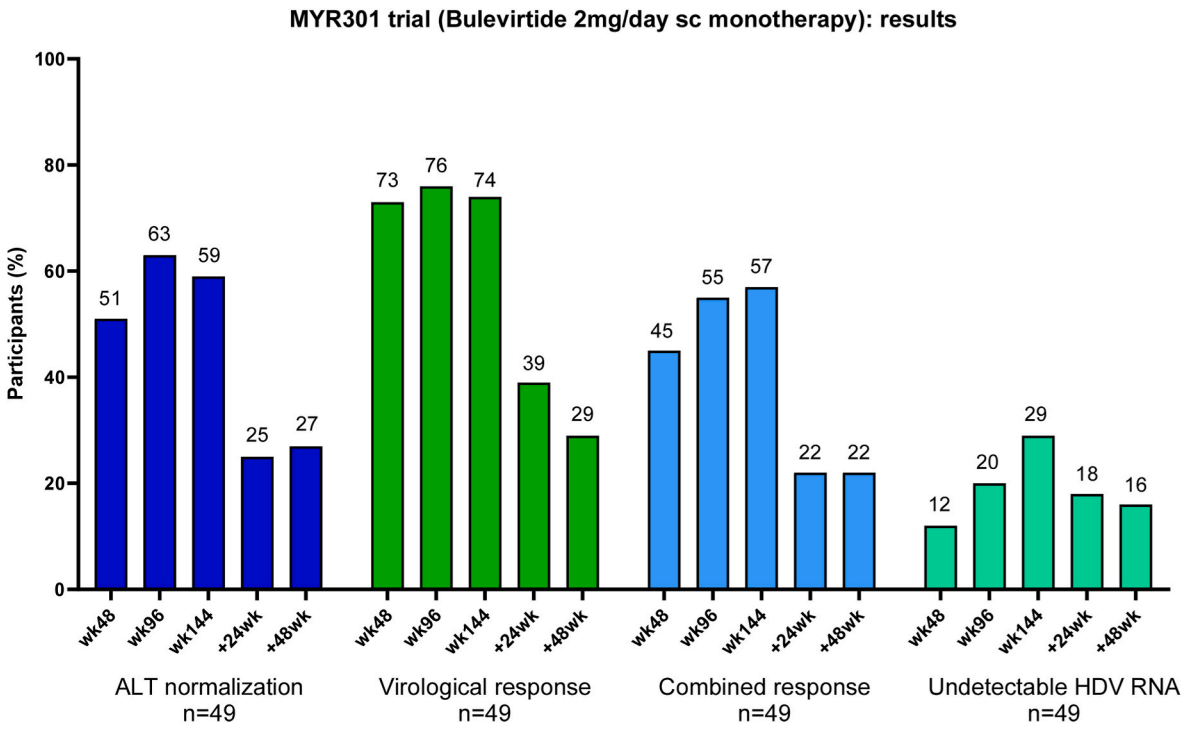

Fig. 3. Results from the phase 3, open-label, randomized trial (MYR 301) of bulevirtide monotherapy in patients with chronic hepatitis D
MYR301 (NCT03852719), a phase 3 randomized study, showed monotherapy with BLV at 2 mg/d or 10 mg/d given subcutaneously was superior to no active anti-HDV treatment based on the combined response (viral response and ALT normalization). Viral response and ALT normalization increase with longer term BLV therapy
HDV RNA levels were quantified by using the RoboGene HDV RNA Quantification Kit, version 2.0 (Roboscreen GmbH, Leipzig, Germany), with lower limits of 50 IU/mL and 6 IU/mL for quantification (LLOQ) and detection (LOD), respectively. Week 96 efficacy responses were improved vs. Week 48. At Week 96, similar combined responses were seen among patients receiving BLV 2 mg/d and BLV 10 mg/d. Viral response and ALT normalization were also similar among patients receiving BLV 2 mg/d and BLV 10 mg/d. No resistance developed to BLV through 96 weeks. No events of HBsAg loss were observed and changes in HBsAg levels were minimal in all treatment arms.

the 10 mg group (P = 0.41). The ALT level normalized in 12 % of patients in the control group, 51 % in the 2 mg group (difference from control, 39 percentage points [95 % confidence interval {CI}, 20 to 56]), and 56 % in the 10 mg group (difference from control, 44 percentage points [95 % CI, 26 to 60]). Loss of HBsAg or an HBsAg level that decreased by at least 1 $\log_{10}$ IU per milliliter did not occur in the BLV groups by week 48. Virological, biochemical and combined responses progressively increased over 3 years of therapy (Wedemeyer et al., 2024). Headache, pruritus, fatigue, eosinophilia, injection-site reactions, upper abdominal pain, arthralgia, and asthenia were more common in the 2-mg and 10-mg groups combined than in the control group. No treatment-related serious adverse events occurred. Dose-dependent increases in bile acid levels were noted in the 2-mg and 10-mg groups. In conclusion, after 48 weeks of BLV treatment, HDV RNA and ALT levels were reduced in patients with CHD. A study based on liver biopsies from the MYR studies, provided evidence that HDV markers of infection decreases also in the liver after 48 weeks of therapies, and that such decrease correlate with the decrease observed in blood (Allweiss et al. J Hepatol. 2024). Eventhough, there is no statistical difference between 2 and 10 mg sc/day, it seems that there is a trend for a better efficacy for 10 mg.

A subset of patients treated with BLV monotherapy (2 mg SC/day) for 2–3 years maintained virological response 24 weeks after stopping BLV. Virological relapse occurred in over half of those participants who were HDV RNA undetectabke at end of treatment and occurred more often in the first 24 weeks after end of treatment (Wedemeyer et al., 2025).

9. MYR-204 clinical trial: Bulevirtide/Pegylated-Interferon combination therapy?

In a phase 2b open-label trial (MYR204, participants were randomly assigned patients to receive pegIFN-a alone (180 μg per week) for 48 weeks; BLV at a daily dose of 2 mg or 10 mg plus pegIFN-a (180 μg per week) for 48 weeks, followed by the same daily dose of BLV for 48 weeks; or BLV at a daily dose of 10 mg alone for 96 weeks (Asselah et al., 2024a). All the patients were followed for 48 weeks after the end of treatment. The primary end point was an undetectable level of HDV RNA at 24 weeks after the end of treatment. The primary comparison was between the 10 mg BLV plus pegIFN-a group and the 10-mg BLV monotherapy group. A total of 24 patients received pegIFN-a alone, 50 received 2 mg and 50 received 10 mg of BLV plus pegIFN-a, and 50 received 10 mg of BLV monotherapy. At 24 weeks after the end of treatment, HDV RNA was undetectable in 17 % of the patients in the pegIFN-a group, in 32 % of those in the 2-mg BLV plus pegIFN-a group, in 46 % of those in the 10 mg BLV plus pegIFN-a group, and in 12 % of those in the 10 mg BLV group (Fig. 4). For the primary comparison, the between-group difference was 34 percentage points (95 % confidence interval, 15 to 50; P < 0.001). At 48 weeks after the end of treatment, HDV RNA was undetectable in 25 % of the patients in the pegIFN-a group, in 26 % of those in the 2 mg BLV plus pegIFN-a group, in 46 % of those in the 10 mg BLV plus pegIFNa group, and in 12 % of those in the 10 mg BLV group. The most frequent adverse events were leukopenia, neutropenia, and thrombocytopenia. Most adverse events were of grade 1 or 2 in severity. Finally, the combination of 10 mg BLV plus pegIFN-a was superior to BLV monotherapy with regard to an undetectable HDV RNA level at 24 weeks after the end of treatment.

Interestingly, no virologic resistance to BLV monotherapy has been

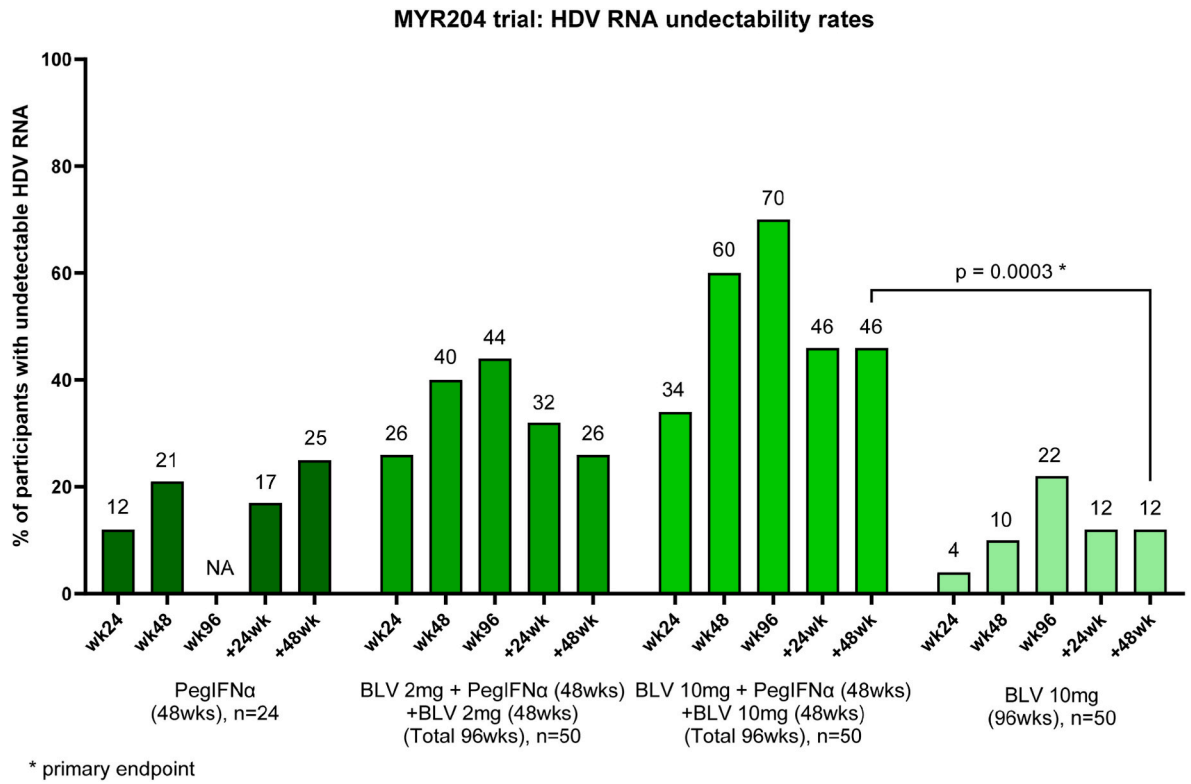

Fig. 4. Results from the randomized trial (MYR 301) of bulevirtide and pegylated interferon combination therapy in patients with chronic hepatitis D
MYR204 is a Phase 2b randomized study conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russian Federation) designed to evaluate the safety and efficacy of finite, 96-week treatment with BLV, with or without PegIFNα, in people living with CHD.
BLV + PegIFNα resulted in greater rates of ALT normalization, HDV RNA undetectability and composite response.
Regarding ALT Normalization, there was a significantly higher rate with BLV 10 mg + PegIFNα vs. BLV 10 mg or PegIFNα monotherapy.
Regarding the composite response, there was a significantly higher rate with BLV 10 mg + PegIFNα vs. BLV 10 mg or PegIFNα monotherapy and a significantly higher rate with BLV 2 mg + PegIFNα vs. BLV 10 mg monotherapy.
Prior PegIFNα exposure was associated with numerically lower response rates with BLV 10 mg + PegIFNα.

detected in patients through 24 weeks treatment in phase II and III clinical trials for CHD (Hollnberger et al., 2023).

There are reports about viral breakthrough during infections. More important, the timing for stopping treatment and follow-up have to be carefully monitored.

10. Safety of Bulevirtide?

The safety and tolerability of BLV were evaluated in an integrated analysis of clinical trial results from CHD patients (Asselah et al., 2024b). Week 48 on-treatment clinical and laboratory results from two Phase 2 trials (MYR203 [NCT02888106] and MYR204 [NCT03852433]) and one Phase 3 trial (MYR301 [NCT03852719]) were pooled (N = 269). Patients were grouped as follows: BLV 2 mg (n = 64), BLV 10 mg (n = 115), pegIFN-a (n = 39) and control (n = 51). The control group consisted of patients assigned to the delayed treatment group in Study MYR301. Adverse events (AEs) that occurred more frequently with BLV 2 mg and BLV 10 mg versus control included increased total bile acid levels (20 % and 17 % vs. 0 %), injection-site reactions (16 % and 20 % vs. 0 %), headache (16 % and 17 % vs. 0 %), pruritus (11 % and 10 % vs. 0 %) and eosinophilia (9 % and 4 % vs. 0 %). Increases in total bile acid levels were observed with BLV without clear correlation with AEs, such as pruritus, eosinophilia or vitamin D deficiency. Grade 3 or 4 study drug-related AEs occurred in a higher proportion of patients receiving pegIFN-a (51 %) than with BLV 2 or 10 mg (3 % and 4 %, respectively). There were no serious AEs related to BLV, and no patients discontinued BLV due to an AE. Neither hepatic decompensation nor death occurred. In conclusion, BLV monotherapy was safe and well tolerated through 48 weeks of treatment in patients with CHD.

11. Real life data for Bulevirtide: similar to clinical trial data?

BLV was approved by the European Medicines Agency (EMA) in 2020 for the treatment of adult patients with CHD and compensated liver disease. Since its approval, real-life data on the use of BLV have been accumulating, with most treated patients in Europe having advanced fibrosis or cirrhosis. Real life data efficacy is concordant to that seen in clinical trials, with many patients achieving significant reductions in HDV RNA levels and ALT normalization after several months of treatment, and favorable safety (De Lédinghen et al., 2024a; Dietz-Fricke et al., 2023; Degasperi et al., 2024). However, HBsAg loss or seroconversion is relatively rare. After 6–12 months of treatment, around 40–60 % achieved more than 2 log reduction in HDV RNA, however a relatively small proportion of patients achieved a complete virological response (undetectable HDV RNA) after 6 months of treatment. It is difficult to summarize these data since real-world evidence is still evolving. Longer-term studies are still required to determine the durability of treatment responses after discontinuation of BLV.

The safety profile in these real-world cases has been consistent with that observed in clinical trials, with few patients discontinuing treatment due to adverse effects. Most adverse events were mild to moderate and included nausea, fatigue, and headache. Injection site reactions (pain, erythema) are the most common side effects, but these are typically mild and transient. Dose-dependent asymptomatic elevations in bile acids were observed with BLV as expected based on mode of action (inhibition of bile acid transporter NTCP). Increases in bile acids

occurred early and remained stable with continued treatment. Bile acids elevations were reversible upon treatment completion. Bile acids elevations were not correlated with pruritus.

Since BLV is administered as a daily subcutaneous injection, patient adherence can be an issue, especially after several years. Early data from clinical trials and real-world studies suggest that BLV may help slow the progression of liver disease in patients with CHD. However, more long-term studies are needed to establish whether it can reverse cirrhosis or prevent hepato-cellular carcinoma. Real life data also have shown some efficacy and favorable safety of off-label BLV in patients with decompensated liver disease (Dietz-Fricke et al., 2024).

Barodelta, a retrospective cohort, evaluated the adherence, persistence, and empowerment of all the patients with chronic HDV infection treated with BLV 2 mg in France and identified via the French National Health Data System (SNDS) (Asselah et al., 2024c). From September 2019 to December 2022, 551 BLV treatments were initiated. The mean age was 42.5 years (±11.4 years), and 69.5 % were male. 46 % received pegIFN-a concomitantly to BLV. Adherence rate was 91 % at 6 months, 89 % at 12 months and 87 % at 24 months. In this real -life French context, it appears that physicians (and patients) prefer a finite therapy strategy, if suitable from the patient profile.

Importantly, real life data have also shown that adults living with HIV coinfected with HDV can be treated by BLV with a virological response in more than 50 % of patients. The combination of BLV and pegIFN-a showed a strong virological response (De Lédinghen et al., 2024b).

Larger studies are important to evaluate the long-term benefits (in terms of HCC, decompensation, survival) and safety of Bulevirtide in diverse populations with different HDV genotypes. After several years of daily injections, there is a fatigue with a risk of lower compliance. It will be also important to explore the potential of combining BLV with other antiviral therapies.

12. Why do we need research to develop drugs for HDV, despite ongoing efforts to develop a cure for HBV?

By definition, as an orphan disease, CHD lacks effective therapies. Whilst there is an important effort to develop a cure for HBV (16–18). There is significant momentum in HBV research to develop therapies to achieve a functional cure for HBV (Yuen et al., 2022, 2023; Nasser et al., 2023). Achieving HBsAg loss after therapy would conceptually provide a cure for HDV. However, the timeline to achieve a cure for HBV is still unknown, and patients with HDV infection need treatment today. HDV is unique in that it causes more severe liver damage than HBV alone, leading to faster progression to cirrhosis, liver failure, and a higher risk of HCC. The available treatments for HBV (such as nucleos(t)ide analogues like tenofovir, tenofovir alafenamide, and entecavir) are effective at suppressing HBV replication but do not significantly impact HDV replication. PegIFN-a has limitations, such as poor tolerability and limited effectiveness, especially in patients with cirrhosis. There is a strong need for direct HDV therapies that could target the viral replication cycle or its interaction with HBV. Finally, the ongoing development of HBV cure drugs does not eliminate the need for specific treatments targeting HDV, given the limited HDV-specific therapies. As such, both HBV cure and HDV-specific treatments are crucial goals to achieve. We need to perform more research, to gain deeper knowledge of the disease complexity (also due to HBV/HDV interactions and presence of HBV integrations which appear to favor HDV persistence (Fig. 5)).

13. Conclusion

CHD is an under-diagnosed and under-estimated disease. Awareness, poor screening and diagnostics have hampered an accurate delineation of the global burden and epidemiology. The lack of widely available, consistent, sensitive viral assays remains problematic. CHD has an accelerated course and can have devastating impact on a relatively young population.

As an orphan disease, the licensing in Europe of BLV is a significant milestone for patients with CHD and health care providers. Effective suppression and normalization of liver function can be expected but ‘infinite’ long term antiviral therapy comes with a high level of patient commitment, monitoring and concordance. Finite therapy of BLV, in combination with pegIFN-a, for those able to tolerate the interferon component, leads to significant durable response.

Further real-world data and newer therapies are required for this disease.

CRediT authorship contribution statement

Tarik Asselah: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Homie Razavi:** Writing – review & editing, Writing – original draft. **Hélène Fontaine:** Writing – review & editing, Writing – original draft. **Kosh Agarwal:** Writing – review & editing, Writing – original draft.

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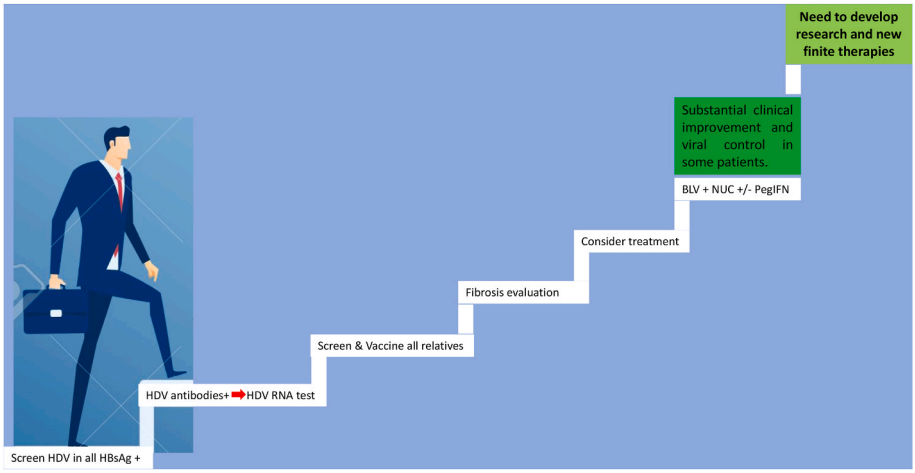

Fig. 5. The patient journey.

on a Data Safety Monitoring from eLilly.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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