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A Decade of Bulevirtide Use in Chronic Hepatitis Delta: Real-World Clinical Results

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ABSTRACT

Background & Aims: Until recently, the only available treatment option for hepatitis D virus (HDV) was the off-label use of interferon, which is associated with limited efficacy and considerable side effects. The approval of the first HDV-direct antiviral, bulevirtide (BLV), has introduced a targeted therapeutic option for patients with chronic hepatitis delta. We assessed the clinical efficacy of BLV in our HDV patients.
Methods: We conducted a retrospective analysis of all patients diagnosed with HDV infection in our department over the past 10 years. For statistical analysis, we performed multivariate analysis of variance, MANOVA.
Results: 26 patients tested positive for HDV antibodies (17 developed chronic hepatitis delta). Eleven patients received BVD. At treatment initiation, liver cirrhosis was present in three patients in the bulevirtide group (MELD-Na: 9–10; Child-Pugh: 5–7) and in three patients in the no bulevirtide group (MELD-Na: 13–18; Child-Pugh: 5–8). Over 12 months of follow-up, bulevirtide recipients showed reductions in alanine aminotransferase (ALT; mean baseline 88 U/L vs 59 U/L; controls 230 U/L vs 206 U/L; MANOVA between-subject effect: $p<0.05$), aspartate aminotransferase (AST; 68 U/L vs 56 U/L; controls 208 U/L vs 151 U/L; $p<0.05$), bilirubin (0.74 mg/dL vs 0.65 mg/dL; controls 1.48 mg/dL vs 1.17 mg/dL; $p<0.005$), HDV-RNA (1,323,182 copies/mL vs 36,975 copies/mL; controls 416,825 copies/mL vs 17,914,733 copies/mL; $p<0.05$) a statistically significant time-by-group interaction was found for both Child-Pugh scores ($p<0.0001$) and MELD-Na scores ($p<0.05$), indicating improved liver function over time in the BLV group compared to controls. No progression of liver fibrosis was observed.
Conclusions: Bulevirtide is a safe and effective treatment for chronic hepatitis delta in a real-world clinical setting. These findings support its role as a sustainable therapeutic option for patients with HDV infection.

Key words: bulevirtide – hepatitis delta – viral hepatitis – real world data – therapeutic options.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BLV: bulevirtide; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HCC: hepatocellular carcinoma; HDV: hepatitis D virus; NTCP: sodium taurocholate cotransporting polypeptide; pegIFN: pegylated interferon.

INTRODUCTION

Hepatitis D virus (HDV) infection has long been recognized as a significant contributor to liver disease [1-4]. According to the World Health Organization (WHO), an estimated 12 million people will be affected by HDV worldwide by 2025. This represents approximately 5% of all individuals who are hepatitis B virus (HBV) positive, forming a relatively small yet clinically important subgroup of patients [5].

Hepatitis D virus infection can manifest as either an acute or chronic condition. The likelihood of developing chronic HDV infection depends largely on the timing of HDV acquisition in relation to HBV infection. In cases of simultaneous coinfection with HBV and HDV - when both viruses are acquired at the same time - the risk of chronicity is approximately lower than 17% [6, 7]. However, in the case of HDV superinfection in individuals with pre-existing chronic HBV infection, the risk of developing a chronic HDV infection increases significantly, ranging from 70% to 90% [8].

Chronic HDV infection is associated with more severe liver pathology compared to HBV monoinfection. It is

linked to increased rates of liver cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality [8, 9]. Due to the progressive nature of the disease, the development of effective therapeutic options is of high clinical interest.

Historically, pegylated interferon (PegIFN) was the only available treatment for HDV. However, its clinical utility is limited by several factors: a lack of robust data to guide optimal treatment duration, the inability to reliably predict treatment response, and a high incidence of adverse effects [9]. Therefore, further research and the development of novel therapeutic agents became essential.

Bulevirtide (BLV), formerly known as myrcludex B, is a peptide entry inhibitor that blocks the interaction between hepatitis B surface antigen (HBsAg) and the sodium taurocholate cotransporting polypeptide (NTCP)—a recently identified receptor responsible for the entry of both hepatitis B virus (HBV) and HDV into hepatocytes [10, 11].

The drug demonstrated safety and efficacy in Phase II and III clinical trials, leading to its conditional approval by the European Medicines Agency (EMA) in July 2020 at a dosage of 2 mg/day administered via subcutaneous injection (EMA Hepcludex authorisation). Full approval was subsequently granted in May 2023 [10]. Bulevirtide has demonstrated both efficacy and safety, even during long-term treatment in patients with compensated liver cirrhosis [10, 12].

In patients treated solely with BLV, an extensive evaluation of both genetic and phenotypic characteristics showed no evidence of resistance-related mutations, neither before starting therapy nor following 24 weeks of treatment [13, 14]. Likewise, prolonged treatment with bulevirtide for up to 96 weeks was associated with a durable virologic response and showed no signs of developing antiviral resistance [10, 15].

Both BLV and PegIFN are administered via subcutaneous injection, which may negatively impact patient compliance. Bulevirtide requires daily administration, whereas PegIFN is given weekly [16, 17]. Despite the more frequent dosing schedule, studies have shown higher compliance rates with BLV compared to PegIFN, possibly due to better drug tolerability and a lower incidence of adverse events [13]. These findings indicate that BLV not only demonstrates a favorable safety and tolerability profile but also maintains a high barrier to resistance, making it an effective therapeutic option that warrants continued clinical monitoring [10, 13].

Further studies have demonstrated that combination therapy with BLV and PegIFN was more effective in reducing HDV RNA to undetectable levels compared to either agent used as monotherapy [2, 7, 18]. Importantly, the frequency of adverse events associated with the combination therapy was not higher than that observed with monotherapy using the same medications [18].

The approval of BLV has marked a significant advancement in the treatment of patients with chronic HDV infection. Early clinical data indicate that the drug is well tolerated, safe, and effective. Initial evidence also suggests an improvement in patient prognosis [10, 15]. However, due to the relatively recent availability of BLV, real-world data remain limited. There is a growing need for observational studies outside of clinical trial settings to better understand its effectiveness and safety in routine clinical practice. We assessed the clinical efficacy of BLV in our cohort of HDV patients.

METHODS

This study was a single-center, retrospective cohort analysis conducted at a German tertiary university hospital. It includes all patients diagnosed and managed for HDV infection in both inpatient and outpatient settings between 2015 and 2025.We conducted an analysis of all patients diagnosed with HDV infection. Relevant cases were identified by searching for the diagnostic term “HDV infection” in our medical records.

Patients with chronic HDV infection were divided into two groups: one receiving treatment with BLV (2 mg per day hereafter referred to as the BVD group) and a cohort without HDV-specific therapy (hereafter referred to as the no BVD group) [17]. The BVL group was compared with the no BVL group at identical follow-up time points, using the same laboratory tests and sonographic examinations. All patients in both groups were treated with tenofovir disoproxil (245 mg daily) for chronic HBV infection [17, 19]. Laboratory assessments included alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-GT, alkaline phosphatase, bilirubin, Quick value, INR, thrombocytes, HBV-DNA, and HDV-RNA.

During each follow-up appointment, patients consulted with a physician to assess symptomatic episodes, medication tolerability, and adverse events.

Sonographic examinations, including assessments for HCC and FibroScan measurements, were performed every six months. FibroScan was performed using shear wave elastography, and all measurements were repeated by trained physicians. Fibrosis stages were classified based on shear wave elastography measurements. F0 (no fibrosis) was defined as measurements up to 1.3 m/s. F1 (mild fibrosis) included measurements up to 1.7 m/s. F2 to F3 (moderate to severe fibrosis) ranged from 1.7 m/s to 2.1 m/s. Measurements exceeding 2.1 m/s were classified as F4 (cirrhosis), with velocities above 2.4 m/s indicating a high risk for portal hypertension.

Follow-up assessments were conducted at baseline and at 3, 6, 12, 18, 24, 30, 36, 42, and 48 months after the initiation of BLV. The first follow-up at three months included a medical examination and laboratory testing, but no sonographic assessment, as sonographic evaluations were scheduled every six months according to guideline recommendations [16, 19-22]. Due to the retrospective nature of the study, follow-up durations varied among patients, as baseline dates differed for each individual.

The study was approved by the Ethics Committee of the University Hospital Regensburg (25-4147-104). It was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Statistical analyses were conducted using SAS® 9.4. Repeated measures MANOVA was employed to evaluate longitudinal laboratory parameters (assessed at four time points) with group (BLV vs. no BLV) as the betweensubjects factor. Due to incomplete data in the no BLV group beyond the fourth time point, a separate repeated measures analysis was

performed exclusively for the BLV group over six time points. In this analysis, a dummy variable was introduced to enable the estimation of withinsubject effects over time. All tests were twotailed with a significance level set at $p<0.05$.

RESULTS

A total of 26 patients were initially screened for study inclusion. Nine patients were excluded due to a history of acute HDV infection that had resolved, with no detectable HDV-RNA at the time of data collection. In these cases, prior HDV infection was confirmed by serological antibody testing; however, the absence of active chronic infection precluded an indication for BLV therapy.

Seventeen patients were diagnosed with chronic HDV infection, confirmed by the presence of measurable HDV-RNA. Among these, 11 patients received BLV treatment and comprised the BLV group (Table I). The remaining six patients did not receive any HDV-specific therapy. Due to lack of follow-up, four out of these six patients served as the no BLV group. The maximum follow-up duration among patients in the BLV group was 48 months.

The gender distribution in our cohort was as follows: in the no BLV group, one female (25%) was included, whereas in the BLV group, four female (36%) were enrolled. Among patients diagnosed with liver cirrhosis (n = 6), three were in the no BLV group (one with liver cirrhosis) and three in the BLV group (two with liver cirrosis). Compared to published data on the gender distribution of HDV infection in Germany, our cohort exhibits a comparable distribution pattern [23].

The no BLV group comprised patients with chronic HDV infection who did not receive BLV treatment, either due to personal preference or clinical contraindications at the time when treatment was considered. One patient declined BLV therapy because of a personal aversion to the subcutaneous route of administration. Another patient, who had initially started BLV treatment, discontinued therapy for personal reasons and was subsequently reassigned to the no BLV group.

In two cases, BLV therapy was withheld due to hydropic decompensated liver cirrhosis, a contraindication, as the drug is not approved for patients with decompensated liver disease [24]. All patients in the BLV and no BLV groups received tenofovir disoproxil as part of standard therapy for chronic HBV infection [16, 19, 20]. The no bulevirtide group comprised four patients, followed for 12 months; three remained till the study ended. All three had liver cirrhosis, including two with hydropic decompensated disease. During follow-up, one control patient was diagnosed with HCC.

At baseline, MELDNa scores for patients with liver cirrhosis ranged from 13 to 18 in the no bulevirtide group and from 9 to 10 in the bulevirtide group. In terms of Child-Pugh scores, baseline values ranged from 5 to 8 in the no bulevirtide group and from 5 to 7 in the bulevirtide group.

The BLV group consisted of 11 patients (4 female), with the longest follow-up duration exceeding 48 months for two patients. The mean age at baseline was 45 years. All patients in the BLV group had measurable HDV-RNA at baseline and were treated with tenofovir disoproxil for HBV infection. At baseline, mean AST and ALT levels were elevated (Table 1). Three patients had compensated liver cirrhosis at baseline, with Child-Pugh scores ranging from A to B. The baseline MELD score ranged from 7 to 10.

Bulevirtide therapy resulted in a marked reduction in HDV-RNA, with most patients achieving undetectable levels (<0 copies/mL). Virologic response was evident by month 3 and persisted throughout follow-up. At 12 months, HDV-RNA levels were significantly lower than in controls (between-subject effect, $p=0.0467$). Over 48 months, HDV-RNA either declined further or remained undetectable, indicating durable viral suppression (Fig 1).

In the BLV group, HDV-RNA declined by month 3 and continued to decrease over 48 months, reaching undetectable levels in most patients. In contrast, HDV-RNA in the no BLV group increased, indicating progressive replication. The between-group difference was significant ($p=0.0467$), favoring BLV (Fig. 1).

Both groups received identical doses of tenofovir disoproxil, supporting that the enhanced HDV-RNA suppression was attributable to BLV. These results underscore its virologic efficacy and potential to improve long-term outcomes in chronic HDV coinfection.

Table I. Characteristics of HVD patients

Characteristics	BLV group (n=11)	No BLV group (n=4)
Mean age at baseline (years), (min, max)	45 (26, 66)	58 (47, 69)
Male gender, n (%)	7 (63.6)	3 (75)
Tenofovirdisoproxil treatment n (%)	11 (100)	4 (100)
Liver cirrhosis, n (%)	3 (27.3)	3 (75)
MELDNa, min-max	9-10	13-18
Child Pugh score, min-max	5-7	5-8
Mean HDV at baseline, copies/mL (min, max)	$1,4x10^6$ ($2,2x10^4$, $7,2x10^6$)	$6,015x10^5$ ($1,2x10^4$, $1,6x10^6$)
Mean HBV at baseline, UI/mL (min, max)	$3,1x10^5$ (0, $3,4x10^6$)	123 (0, 360)
Mean AST at baseline, U/L (min, max)	68 (34, 145)	245 (91, 580)
Mean ALT at baseline, U/L (min, max)	88 (43, 299)	321 (69, 681)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BLV: bulevirtide; HBV: hepatitis B virus; HDV: hepatitis D virus; MELDNa: model for end-stage liver disease sodium.

In this cohort, the maximum follow-up period extended to 48 months, with two patients in the BLV group completing the full observation window. A decline in HDV-RNA became apparent as early as three months after treatment initiation and continued steadily over time. This sustained reduction ultimately resulted in HDV-RNA normalization in the majority of patients receiving BLV. Strikingly, none of the initial responders experienced viral rebound during the entire 48-month period, suggesting that long-term BLV therapy was not associated with the emergence of viral escape variants (Fig. 1).

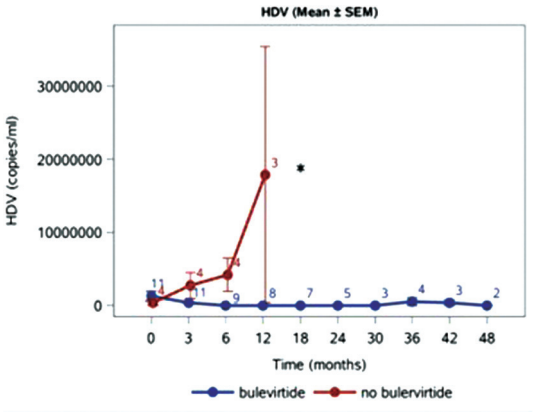

Fig 1. HDV RNA levels during follow-up in the bulevirtide (BLV) group and the no BLV group. *p<0.05 MANOVA between-subject effect; time points 0, 3, 6, and 12 months were considered as repeated measurements. The number next to each circle indicates the number of patients.

Normalization of transaminases was also achieved during bulevirtide therapy, reflecting a reduction in hepatocellular injury. AST levels exhibited a significant between-subject effect (p=0.0110), while ALT levels showed both a significant between-subject effect (p=0.0105) and a time-by-group effect (p=0.0142) (Figs. 2a and 2b). AST and ALT levels, serving as biomarkers of hepatocellular injury, demonstrated parallel trajectories over the follow-up period. In the no BLV group, an initial decline in transaminase levels was followed by a subsequent increase, consistent with progressive liver damage in the absence of HDV-targeted therapy. In contrast, patients receiving BLV exhibited stabilization and eventual normalization of AST (Fig. 2a) and ALT (Fig. 2b) levels, indicating a sustained reduction in hepatic injury during treatment.

In addition to sustained virologic suppression and normalization of transaminases, BLV therapy was associated with favorable changes in liver function parameters. Bilirubin levels, however, demonstrated a significant decline over time, with both a between-subject effect (p=0.0031) and a time-by-group interaction (p=0.0482) (Fig. 3). Quick values (Fig, 4a) and INR (Fig. 4b) showed trends toward improvement, although these did not reach statistical significance for within- or between-subject effects.

Together with the improvements in bilirubin, these findings provide robust evidence for the long-term therapeutic efficacy of BLV in patients with chronic HDV coinfection. Taken together, the parallel improvements in virologic suppression and liver function parameters highlight the comprehensive clinical benefit achieved with sustained BLV treatment.

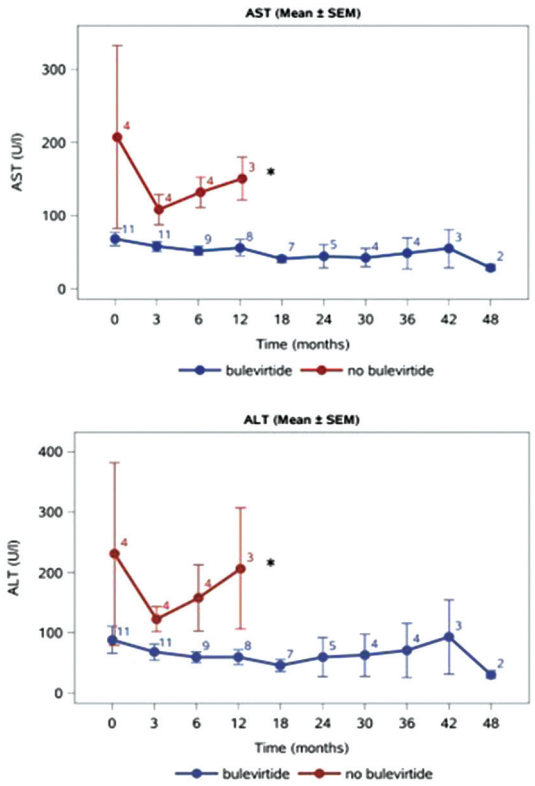

Fig. 2. Transaminases levels during follow-up.

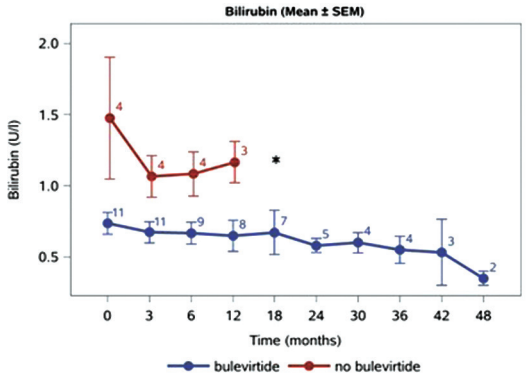

Fig. 3. Bilirubin levels during the observation period.

These results were further emphasized by the fact that no worsening of liver stiffness was observed, as measured by shear wave elastography (Fig. 5).

Collectively, these findings support the long-term efficacy of bulevirtide in chronic HDV coinfection, with consistent improvements in liver disease parameters across multiple clinical and biochemical markers.

In our cohort, sonographic examinations, including shear wave elastography, were performed every six months to monitor liver stiffness. At treatment initiation, three patients in the BLV group and three in the no BLV group had compensated cirrhosis and therefore did not undergo elastography. As a result, liver stiffness measurements were only available for non-cirrhotic patients in the BLV group, while most patients in the no BLV group were not assessed due to the high prevalence of cirrhosis. During follow-up, liver stiffness remained stable in the BLV group, with no evidence of progression (Fig. 5).

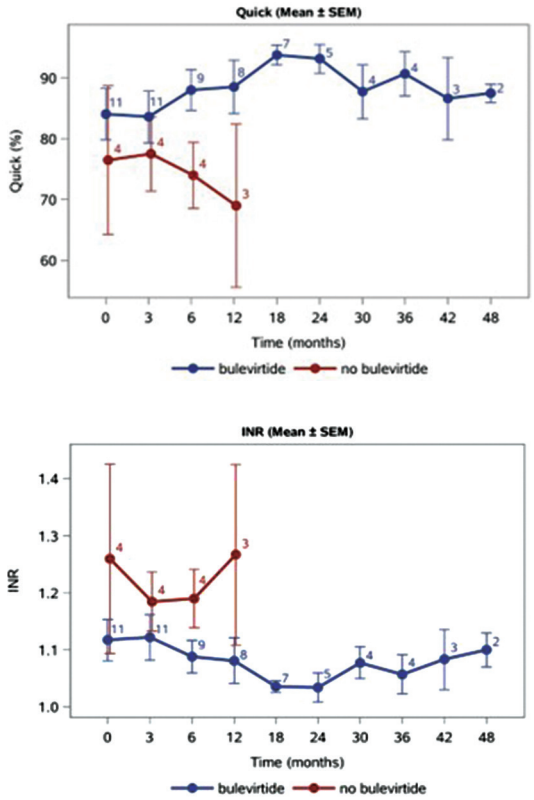

Fig. 4. Protrombine time (Quick time((a) and INR (b) during the observation period.

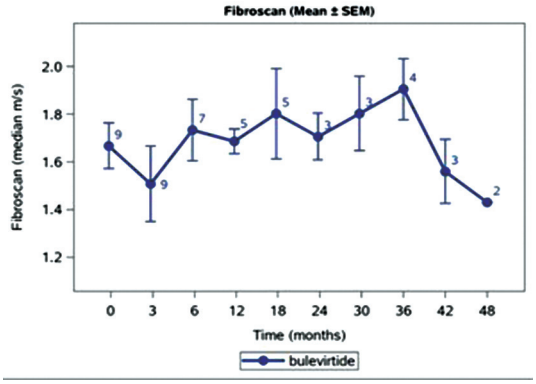

Fig. 5. Median liver stiffness in the BLV group.

These findings suggest that BLV therapy may contribute to the stabilization of liver fibrosis in non-cirrhotic patients with chronic HDV infection.

At baseline, MELD-Na scores among patients with liver cirrhosis ranged from 13 to 18 in the no BLV group and from 9 to 10 in the BLV group. Corresponding Child-Pugh scores ranged from 5 to 8 in the no BLV group and from 5 to 7 in the BLV group.

In this cohort, BLV therapy not only stabilized hepatic function over time but also led to measurable improvements in cirrhosis stage. Over the 12-month follow-up, patients receiving BLV exhibited a reduction in MELD-Na scores (Fig. 6a) and sustained improvement or stabilization in Child-Pugh scores (Fig. 6b).

Conversely, untreated cirrhotic patients showed a progressive increase in MELD-Na scores (Fig 6a) and deterioration in Child-Pugh scores (Fig. 6b), consistent with advancing liver dysfunction.

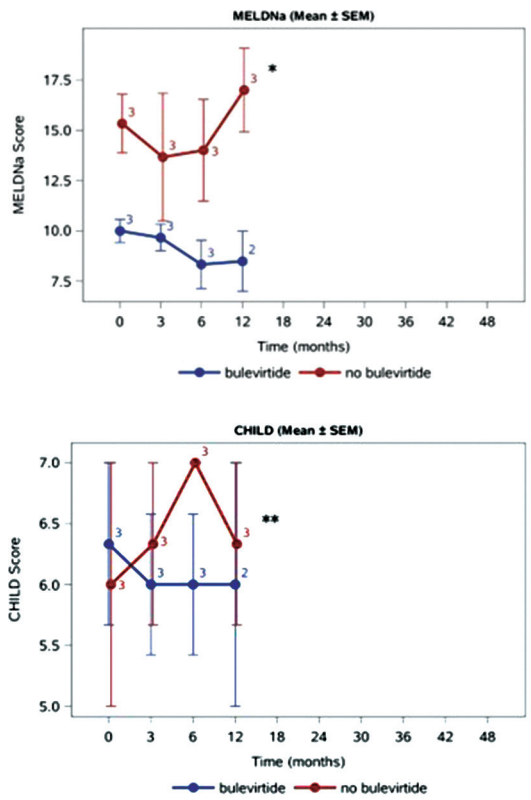

Fig. 6. MELDNa (6a) and Child-Pugh scores (6b) in patients with liver cirrhosis.

These changes were statistically significant, with a time-by-group interaction observed for both Child-Pugh scores ($p<0.0001$) and MELD-Na scores ($p=0.0428$).

In this study, the prevalence of liver cirrhosis was significantly higher in the no BLV group compared to the BLV group (75% vs. 27%). The no BLV group also demonstrated more advanced liver disease at baseline. During follow-up, progressive hepatic deterioration was observed exclusively in the no BLV group, as indicated by increasing AST and ALT concentrations (Fig. 2), elevated INR and bilirubin levels and declining prorombin time values (Figs. 3, 4).

In contrast, the BLV group demonstrated AST and ALT levels declined progressively and normalized during the study period (Fig. 2) and furthermore a stabilization and subsequent improvement in liver function over time, as reflected by improved bilirubin levels, Quick values and reductions in INR (Figs. 3, 4).

DISCUSSION

Our results suggested that early initiation of BLV in HDV coinfection (particularly during the compensated stage of liver disease) resulted in sustained improvements in liver biochemical and functional parameters, in contrast to the progressive deterioration observed in the untreated no BLV group.

Our data confirm previous evidence indicating that hepatitis D virus (HDV) infection continues to represent a clinically significant cause of progressive liver injury, often resulting in hepatic decompensation and HCC despite antiviral

co-management [2]. However, recent advances in antiviral therapy have significantly improved the management of this disease. The approval of BLV, as well as its use in combination with PegIFN, offers new therapeutic strategies with promising efficacy [15, 18]. These developments mark a turning point in the treatment landscape of chronic HDV infection, making it increasingly controllable and, in some cases, potentially curable [7]. This progress allows for a more optimistic outlook for affected patients, a development that is further supported by the findings from our real-world cohort.

Similar to our cohort, other real-world studies have demonstrated a significant reduction in HDV-RNA levels, which is associated with improved clinical outcomes due to a reduced risk of disease progression, including liver cirrhosis and HCC [24-26]. Additionally, our data and findings from other cohorts show a decrease in serum transaminases (ALT and AST), indicating reduced hepatocellular injury [24, 25].

Beyond antiviral efficacy, BLV improves liver function parameters such as bilirubin, prothrombin time, and INR, indicating preserved hepatic function and reduced risk of decompensation. These effects, likely reflecting its anti-inflammatory activity, position BLV as a major advance in chronic HDV therapy, providing durable virological, biochemical, and functional benefits - findings that are consistent with previous reports and supported by our real-world data [27].

Despite its promise, BLV therapy still has limitations. Evidence from other real-life cohorts indicates that loss of hepatitis B surface antigen (HBsAg) remains rare during treatment [25]. Given that HDV replication requires the presence of HBsAg, patients who do not achieve HBsAg loss remain at risk of viral relapse upon discontinuation of BLV therapy [3, 4, 25, 28].

The optimal duration of BLV therapy in patients with chronic HDV infection remains an open question [27, 29, 30]. Current guidelines recommend continuous treatment in the absence of contraindications or adverse events [17]. However, a limited number of studies have investigated the appropriate length of therapy. Notably, Jachs et al. [31] provided valuable insights by evaluating outcomes in patients who discontinued BLV treatment. Among seven patients studied, one was lost to follow-up, and four experienced a relapse of detectable HDV RNA between 24 weeks and one year after treatment discontinuation. Interestingly, two patients showed no evidence of relapse and maintained undetectable HDV RNA levels. Both had previously received combination therapy with BLV and PegIFN [31], suggesting a potential benefit of combination treatment in achieving sustained virological response [29]. This has also been shown by a systematic review and network meta-analysis confirming that combination therapy with BLV and PegIFN achieved superior virological outcomes and higher composite response rates compared with either agent alone [30]. In our cohort, this question could not be addressed, as none of the patients discontinued BLV therapy during the observation period. Nevertheless, determining the optimal duration of BLV treatment remains a crucial issue and should be the focus of future prospective studies.

This study provides important real-world evidence on the clinical use of bulevirtide in patients with chronic HDV infection, including individuals with advanced liver disease who are typically underrepresented in clinical trials. The inclusion of unselected patients reflects routine clinical practice, thereby increasing the external validity and generalizability of the findings. Comprehensive longitudinal follow-up enabled detailed assessment of both virological and biochemical responses, as well as dynamic changes in liver function and surrogate markers of fibrosis.

As a retrospective cohort study, data acquisition was inherently subject to variability in clinical documentation and missing data, which may have introduced selection and information bias. Comparisons between treated and untreated patients were limited by marked differences in baseline disease severity, precluding direct comparability between groups and restricting causal inference regarding treatment efficacy. Moreover, the follow-up duration was relatively short, preventing robust conclusions about long-term clinical outcomes such as transplantation-free survival, liver-related mortality, and hepatocellular carcinoma incidence. Finally, the sample size - particularly within the cirrhotic subgroup - may have limited the statistical power to detect small but clinically relevant effects.

CONCLUSIONS

Bulevirtide demonstrates a favorable safety and efficacy profile in patients with chronic HDV infection, showing effectiveness in both non-cirrhotic and cirrhotic individuals. In our real-world cohort, treatment resulted in a sustained decline in HDV RNA levels, accompanied by consistent improvements in serum AST, ALT, and bilirubin concentrations, indicating reduced hepatic inflammation and preserved liver function. No progression of hepatic fibrosis was observed, and patients with cirrhosis exhibited improvements in both Child–Pugh and MELD-Na scores. Overall, bulevirtide demonstrates clinically meaningful therapeutic benefits across the disease spectrum, with early initiation likely contributing to long-term disease stability and improved prognosis. Its use should be strongly considered in all patients with chronic HDV infection. Further studies are warranted to elucidate treatment outcomes in decompensated cirrhosis and to assess the long-term impact on overall survival, liver-related mortality, and hepatocellular carcinoma risk.

Conflicts of interest: None to declare.

A**uthors' contributions**: S.R. and M.M. conceived the study. All the authors collected and analyzed the data and drafted the manuscript. S.R. and M.M. critically revised the manuscript. All the authors read and approved the final version of the manuscript.

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