

Treating hepatitis D with bulevirtide – Real-world experience from 114 patients

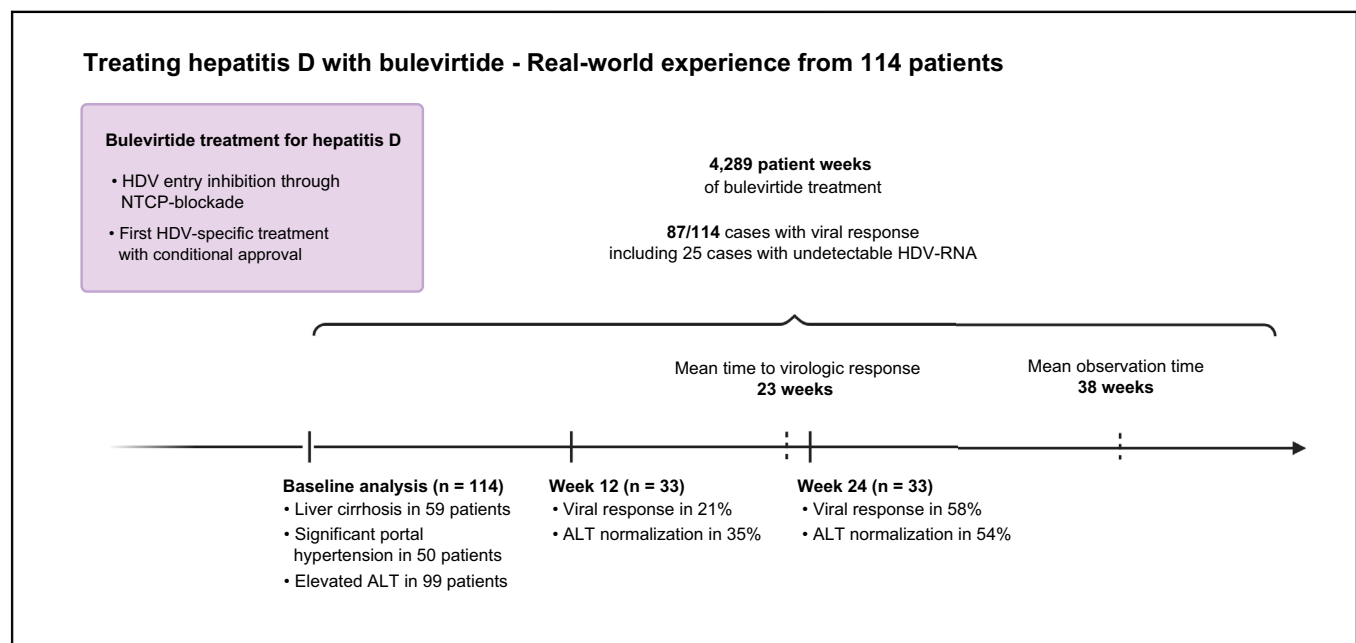
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Graphical abstract



Highlights

- 114 patients were treated with bulevirtide under real-world conditions, including 50 with signs of significant portal hypertension.
- A virologic response was observed in 87/114 patients, with 25 patients achieving HDV-RNA negativity.
- ALT levels improved regardless of virologic response status.
- In a small subgroup of patients with decompensated liver disease, bulevirtide treatment appeared to be safe.

Impact and implications

Clinical trials proved the efficacy of bulevirtide for chronic hepatitis D and led to conditional approval by the European Medical Agency. Now it is of great interest to investigate the effects of bulevirtide treatment in a real-world setting. In this work, we included data from 114 patients with chronic hepatitis D who were treated with bulevirtide at 16 German centers. A virologic response was seen in 87/114 cases. After 24 weeks of treatment, only a small proportion of patients did not respond to treatment. At the same time, signs of liver inflammation improved. This observation was independent from changes in hepatitis D viral load. The treatment was generally well tolerated. In the future, it will be of interest to investigate the long-term effects of this new treatment.



Treating hepatitis D with bulevirtide – Real-world experience from 114 patients

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Background & Aims: Bulevirtide is a first-in-class entry inhibitor of hepatitis B surface antigen. In July 2020, bulevirtide was conditionally approved for the treatment of hepatitis D, the most severe form of viral hepatitis, which frequently causes end-stage liver disease and hepatocellular carcinoma. Herein, we report the first data from a large multicenter real-world cohort of patients with hepatitis D treated with bulevirtide at a daily dose of 2 mg without additional interferon.

Methods: In a joint effort with 16 hepatological centers, we collected anonymized retrospective data from patients treated with bulevirtide for chronic hepatitis D.

Results: Our analysis is based on data from 114 patients, including 59 (52%) with cirrhosis, receiving a total of 4,289 weeks of bulevirtide treatment. A virologic response defined as an HDV RNA decline of at least 2 log or undetectable HDV RNA was observed in 87/114 (76%) cases with a mean time to virologic response of 23 weeks. In 11 cases, a virologic breakthrough (>1 log-increase in HDV RNA after virologic response) was observed. After 24 weeks of treatment, 19/33 patients (58%) had a virologic response, while three patients (9%) did not achieve a 1 log HDV RNA decline. No patient lost hepatitis B surface antigen. Alanine aminotransferase levels improved even in patients not achieving a virologic response, including five patients who had decompensated cirrhosis at the start of treatment. Treatment was well tolerated and there were no reports of drug-related serious adverse events.

Conclusions: In conclusion, we confirm the safety and efficacy of bulevirtide monotherapy in a large real-world cohort of patients with hepatitis D treated in Germany. Future studies need to explore the long-term benefits and optimal duration of bulevirtide treatment.

Impact and implications: Clinical trials proved the efficacy of bulevirtide for chronic hepatitis D and led to conditional approval by the European Medical Agency. Now it is of great interest to investigate the effects of bulevirtide treatment in a real-world setting. In this work, we included data from 114 patients with chronic hepatitis D who were treated with

Keywords: Hepatitis D; Viral hepatitis; Bulevirtide; Real world experience; Antiviral treatment.

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bulevirtide at 16 German centers. A virologic response was seen in 87/114 cases. After 24 weeks of treatment, only a small proportion of patients did not respond to treatment. At the same time, signs of liver inflammation improved. This observation was independent from changes in hepatitis D viral load. The treatment was generally well tolerated. In the future, it will be of interest to investigate the long-term effects of this new treatment.

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Introduction

Hepatitis D is the most debilitating form of viral hepatitis and is associated with a rapid progression towards cirrhosis and a substantial increase in risk of hepatocellular carcinoma (HCC) development.^{1,2} Hepatitis D virus (HDV) infection requires prior or simultaneous infection with hepatitis B virus (HBV), as the assembly of HDV is dependent on the hepatitis B surface antigen (HBsAg). Worldwide an estimated 9–19 million patients are assumed to be coinfecting with HDV.³ HDV infection is associated with a remarkable increase in liver-related morbidity and mortality, causing a significant global health burden.^{4–6} Persistent inflammation causes liver tissue damage, eventually leading to liver fibrosis and cirrhosis. Within 5–10 years after diagnosis up to 70% of infected individuals are likely to develop cirrhosis.¹ A meta-analysis comparing the HCC risk in HBV-monoinfected and HBV/HDV-coinfected individuals revealed odds ratios ranging between 1.25 and 2.77, emphasizing the increased risk of HCC in case of HDV infection.⁷

The hepatitis D antigen was described for the first time in 1977.⁸ In 1986 the genome was discovered and HDV was shown to be a single-stranded RNA virus.⁹ The viral genome encodes for the small delta antigen and the large delta antigen.¹⁰ While the small delta antigen is assumed to play a role in viral replication, the large delta antigen is involved in viral assembly.¹¹ The envelope of HDV consists of the HBsAg proteins, making the transmission of HDV HBV-dependent. Therefore, the interaction of HBsAg with the sodium taurocholate cotransporting polypeptide (NTCP) – a specific bile salt transporter – is crucial for the entry of HDV virions into hepatocytes¹² and is the basis for treatment with bulevirtide (an HDV entry inhibitor).

Historically, HDV infection was treated with interferon-based therapies.¹³ Treatment of viral hepatitis with interferon alfa does not represent a specific antiviral therapy but promotes distinct effects on hepatocytes and different immune cells. Despite well-known side effects, the efficacy of interferon treatment is limited. Overall, 30–40% of patients achieve undetectable HDV RNA during treatment, but early and late relapses after interferon treatment have been reported.¹⁴ Long-term observation of HDV-infected patients revealed that the risk of liver transplantation and hepatic decompensation was lower in patients treated with an interferon-alfa-based therapy than in those receiving nucleos(t)ide analogues (NAs) alone.^{15–19} Even though interferon treatment improved the chance of losing HDV RNA, treatment efficacy is not satisfactory. Moreover, only a proportion of patients can be treated with pegylated interferon alfa (PEG-IFNa) due to a variety of contraindications.

The conditional approval of bulevirtide as an entry inhibitor was based on results from phase II clinical trials.²⁰ Overall, these studies suggested that bulevirtide treatment leads to continued HDV RNA decline and improvements of biochemical disease activity. Tolerability and safety were considered good. Since 2020, some “real-world” experiences with small case series from Italy,²¹ France,²² Austria²³ and Germany^{24,25} have been reported as full papers. Additional cohorts were presented during recent

scientific meetings.²⁶ These reports provided heterogenous data on virologic efficacy, rates of virologic non-response, and biochemical improvements during treatment.

In Germany, since September 2020, physicians experienced in the treatment of hepatitis D have been able to prescribe bulevirtide. Herein, we provide the first data from a retrospective data collection on patients with hepatitis D treated with bulevirtide at a daily subcutaneous dose of 2 mg without additional PEG-IFNa. To our knowledge, this is the largest cohort of patients treated outside of clinical trials or distinct early access programs.

Patients and methods

Data was collected from German hepatological centers and outpatient clinics treating patients with 2 mg of bulevirtide. Retrospective data were shared after anonymization and collected in a central data sheet. The ethics committee of Hannover Medical School approved the protocol for the retrospective analysis (ethical approval number 10161_BO_K_2022).

Laboratory results are all based on local results from each participating center. Because of differences in HDV RNA assays, a direct comparison of the absolute individual viral loads was not possible. However, individual viral kinetics were analyzed after log-transformation. Virologic response was assumed when a ≥ 2 log decline from baseline occurred or HDV RNA was undetectable or below the lower limit of quantification. Virologic non-response was defined as a maximum decrease of HDV RNA by 1 log or an increase. A decline of HDV RNA by more than 1 log but less than 2 log was classified as an intermediate virologic response. Virologic breakthrough was defined as an increase by ≥ 1 log after virologic response. Cirrhosis was assumed if confirmed by liver histology or based on the following clinical parameters if no histology was available: presence of esophageal varices, platelets below 100,000/ μ l or transient elastography of ≥ 15 kPa.

Patients could be included if treatment of chronic HDV infection was initiated with a daily dose of 2 mg bulevirtide without additional application of PEG-IFNa. A second inclusion criterion was detectable HDV RNA at baseline. Cases with missing baseline information on HDV RNA and/or alanine aminotransferase (ALT) were excluded from the analysis. In analogy to clinical trial protocols²⁰ and to reproduce trial results in a real-world setting, we also investigated response criteria at distinctive time points (baseline, week 12 and 24) even though only a subset of patients had data available at all three time points. The analysis of endpoints at week 12 and 24 was based on cases with no missing values in the variables displayed. Separate subsets were created for the analysis of changes in liver stiffness and IgG as these were not available for all patients.

All statistical tests were carried out with R version 1.2.1335.^{27,28} Statistical significance was assumed when the *p* value was below 0.05. Given the retrospective nature of this work there was no prior definition of sample size. Our aim was to collect as much data as possible from the participating centers.

Table 1. Baseline patient characteristics.

Baseline patient characteristics (N = 114)	
Age, mean \pm SD	47 \pm 11
Male/female	80/34 (70%/30%)
Cirrhosis	59 (52%)
FibroScan >15 kPa	22
Esophageal varices	31
Histologically confirmed	8
Platelets <100,000/ μ l	44
Child-Pugh grade	
Child-Pugh A	54
Child-Pugh B	4
Child-Pugh C	1
FIB-4, median	2.9
Below 1.3	12%
Above 2.67	52%
Fibroscan® kPa, median (n = 40)	15.9
Above 25 kPa	18%
Below 10 kPa	22.5%
BMI, median (n = 98)	26
ALT U/L, mean \pm SD	115 \pm 102
Albumin g/L, mean \pm SD (n = 111)	41 \pm 6
Below 35 g/L, %	17%
Bilirubin μ mol/L, mean \pm SD	15 \pm 10
Platelets $\times 10^3/\mu$ l, median	122
Treatment with NAs (n = 113)	108 (96%)
Tenofovir disoproxil	71
Entecavir	16
Previous PEG-IFNa treatment (n = 110)	55 (50%)

Data are presented as n or n (%) unless otherwise stated.

Shown are characteristics of 114 patients included in the retrospective analysis of bulevirtide treatment for chronic hepatitis D. The sample size for each variable is provided in parentheses if deviant from 114.

ALT, alanine aminotransferase; FIB-4, fibrosis-4; NA, nucleos(t)ide analogues; PEG-IFNa, pegylated interferon alfa.

For the comparison of baseline and follow-up weeks, a paired *t* test and Wilcoxon-signed-rank-test for non-parametric data were used, respectively. Longitudinal data were compared using a repeated-measurement ANOVA. Individual patients served as between subject factor, treatment weeks served as within subject factor and indicator for a significant change during the observational period. Bonferroni-corrected paired *t* tests were used for *post hoc* comparisons. A univariate ANOVA with *post hoc* Tukey test was used for the comparison of baseline characteristics of patients with and without virologic response. Figures were created with R version 1.2.1335 and [Biorender.com](https://www.biorender.com).

Results

In total, data from 121 cases were available for retrospective analysis. In seven cases, missing baseline information on ALT

and/or HDV RNA led to exclusion from the analysis; thus, the final analysis was based on data from 114 patients. Clinical characteristics are summarized in [Table 1](#). The majority of patients selected for bulevirtide treatment had advanced liver disease, with 52% meeting criteria for the presence of cirrhosis. Esophageal varices were reported for 31 patients and 44 patients had platelet levels below 100,000/ μ l. Overall, 50 patients had evidence of significant portal hypertension based on either one of these criteria. Hepatic decompensation at treatment initiation was present in five cases (Child-Pugh B: n = 4; Child-Pugh C: n = 1; outcome of these patients is reported below). In 99/114 patients, ALT was elevated (>35 IU/L in female, > 45 IU/L in male patients), indicating relevant hepatic inflammation. Bulevirtide was given almost exclusively in combination with NAs and 50 patients had been treated with PEG-IFNa before. Following the exclusion criterium of this analysis, no patient included here received bulevirtide in combination with PEG-IFNa. We did not perform HDV genotyping. However, our study population was dominated by patients of Caucasian origin (n = 85) and, as known from epidemiological studies, HDV genotype 1 is the predominant genotype in the northern hemisphere.⁴

Overall, this analysis included 4,289 patient weeks of bulevirtide treatment ([Fig. S1](#)). The mean observation time was 38 \pm 17.6 weeks. During this time a virologic response (namely an HDV RNA decline of at least 2 log IU/ml) was observed in 87/114 cases. Undetectable HDV RNA was achieved in 25 cases. The mean time to virologic response was 23 weeks. In 11 cases, a virologic breakthrough (≥ 1 log-increase in HDV RNA after virologic response) was observed. In 33 patients, viral response could be investigated at week 12 and 24 ([Table 2](#)). At week 12, viral response was observed in 7/33 (21%) and at week 24 in 19/33 (58%) patients. In contrast, 9/33 (27%) and 3/33 (9%) patients had not reached a 1 log HDV RNA decline, respectively. Viral kinetics and ALT dynamics of the three cases with virologic non-response at week 24 are shown in [Fig. 1](#). While a decline of ALT levels was only transient in one case, the two remaining cases showed persistent improvements.

In the 87/114 cases with viral response, the ALT had decreased by 67 IU/L at the time point of viral response. ALT kinetics were analyzed in more detail at week 12 and week 24. ALT levels decreased significantly within the first 12 weeks of treatment. Interestingly, a significant decline of ALT at week 12 and 24 was also seen in cases without virologic response. Baseline ALT levels were higher in those without virologic response at week 12 ([Fig. 2A](#)). ALT normalization was defined as a decrease below 35 IU/L for female and below 45 IU/L for male patients. Elevated ALT levels at baseline were measured in 26/33 patients. At week 12

Table 2. Comparison of disease characteristics at baseline and after 12 and 24 weeks of bulevirtide treatment.

Patient characteristics (n = 33)	Baseline	Week 12	Week 24	Post hoc <i>p</i> value
Virologic response, n (%)	—	7/33 (21%)	19/33 (58%)	
Virologic non-response, n (%)	—	9/33 (27%)	3/33 (9%)	
ALT U/L, mean \pm SD	114 \pm 73	53 \pm 35	47 \pm 32	<0.001*
Mean ALT change U/L \pm SD	—	-61 \pm 55	-68 \pm 66	<0.001**, 0.627***
Albumin g/L, mean \pm SD	41 \pm 5	41 \pm 6	42 \pm 6	No post hoc test, ANOVA <i>p</i> = 0.237
Below 35 g/L, %	12%	15%	9%	
Bilirubin μ mol/L, mean \pm SD	14 \pm 9	14 \pm 11	14 \pm 11	No post hoc test, ANOVA <i>p</i> = 0.712
Platelets $\times 10^3/\mu$ l, median	133	149	157	No post hoc test, ANOVA <i>p</i> = 0.104

*Baseline vs. week 12, **baseline vs. week 24, ***week 12 vs. week 24.

Data points from baseline, week 12 and 24 were compared with repeated-measurement ANOVA and *post hoc* Bonferroni-corrected *t* tests. *p* values <0.05 were assumed statistically significant.

ALT, alanine aminotransferase.

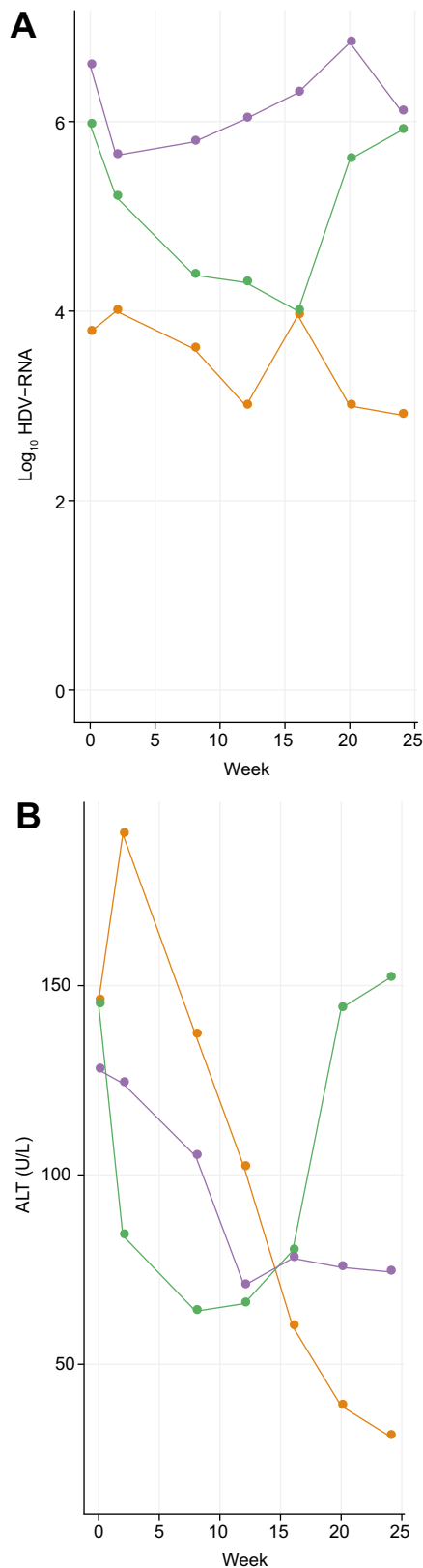


Fig. 1. Viral kinetics and ALT decline in patients with virologic non-response at week 24 (n = 3). Displayed are individual HDV RNA and ALT levels of three patients with virologic non-response (<1-log-reduction) at week 24. Each patient is symbolized by a color. ALT, alanine aminotransferase.

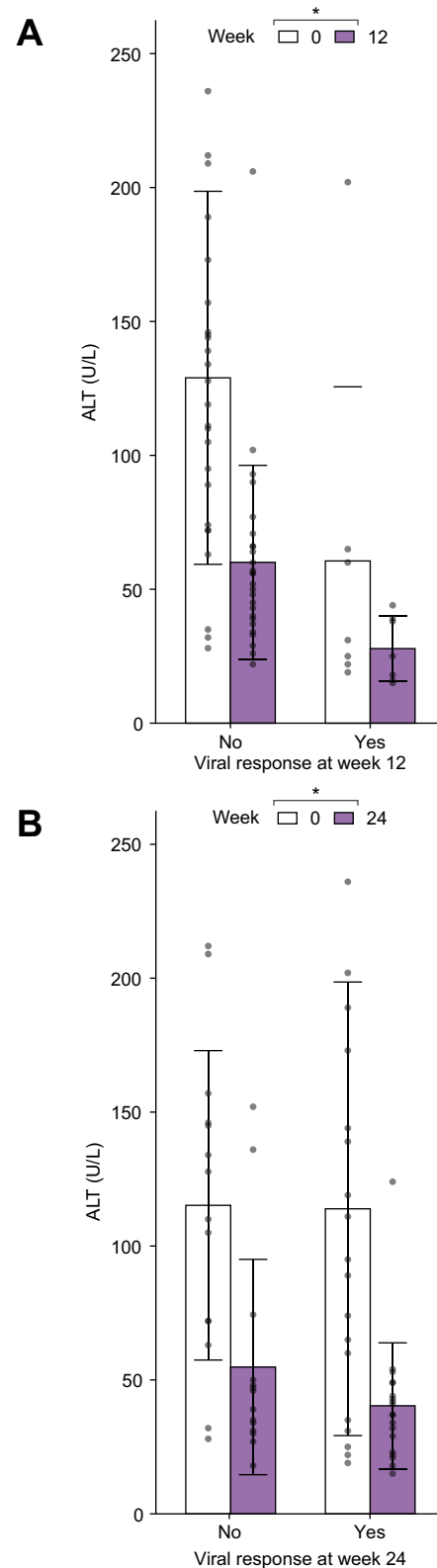


Fig. 2. Change in ALT levels grouped by virologic response at week 12 and week 24 (n = 33). (A) Patients who achieved a virologic response at week 12 and (B) those who achieved a virologic response at week 24. Bars represent mean ALT levels at week 0 (white), week 12 (grey) and week 24 (dark grey). Error bars show the SD. Individual data points are visualized by dots. Wilcoxon signed-rank tests were used for comparison of ALT at week 0 and 12 or 24; **p* < 0.05. ALT, alanine aminotransferase.

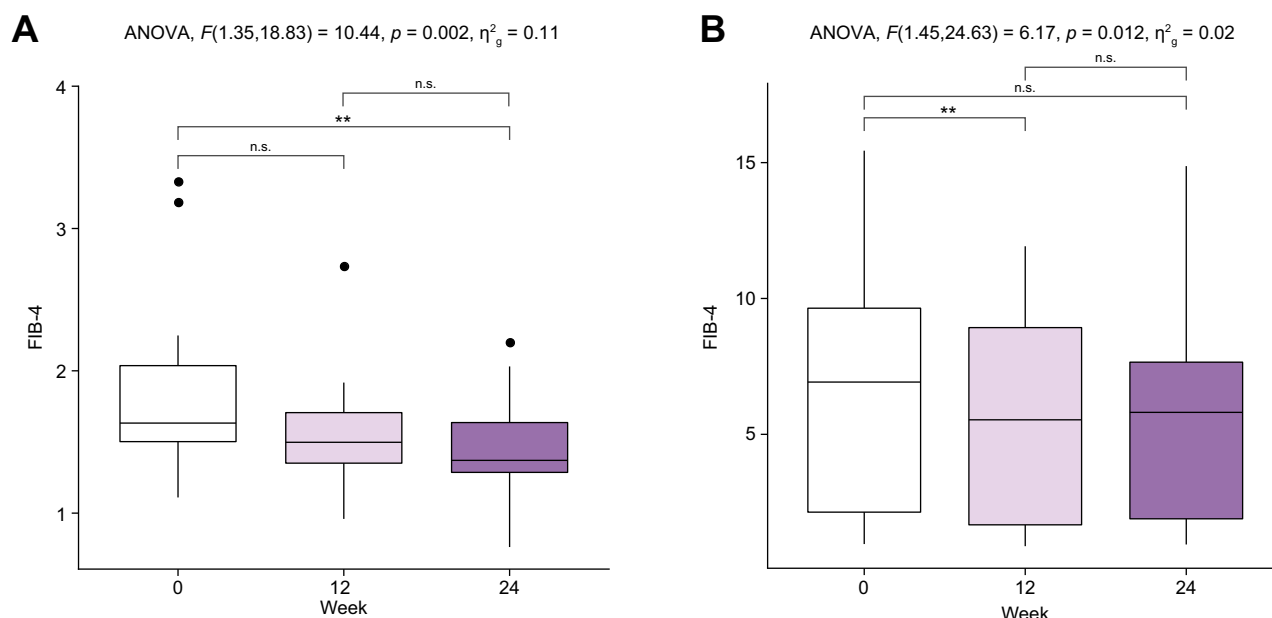


Fig. 3. FIB-4 values at week 0, 12, 24 in patients without cirrhosis and with cirrhosis (n = 33). (A) Patients without cirrhosis and (B) patients with cirrhosis. Shown are boxplots of FIB-4 values of 33 patients at the three time points. Patients are grouped according to the presence of cirrhosis. Data were analyzed with a repeated-measurement ANOVA and *post hoc* Bonferroni-corrected paired *t* tests. **p* < 0.05.

and 24, ALT had normalized in 9/26 and 5/26 of patients, respectively.

To investigate predictors for viral response at week 12 and week 24 we compared baseline characteristics of respective responders and non-responders as well as patients with intermediate viral responses (Table 3). However, there were no differences in the selected variables ALT, age at baseline and the presence of cirrhosis.

A loss of HBsAg did not occur. Quantitative HBsAg was measured in a subset of 20 patients. A decline of >1 log HBsAg IU/ml did not occur. While HBsAg levels slightly increased between week 0 (14,635 IU/ml \pm 15,006) and 12 (16,726 \pm 17,533; *p* = 0.032), this observation could not be made between week 0 and 24 (15,011 IU/ml \pm 18,975; *p* = 0.426).

Fibrosis-4 (FIB-4) values also showed a significant decline during bulevirtide treatment (Fig. 3). This was observed in patients without cirrhosis (Fig. 3A) and with cirrhosis (Fig. 3B). The *post hoc* test demonstrated a significant decline in FIB-4 score between week 0 to 12 (*p* = 0.007) in patients with cirrhosis (Fig. 3B). In patients without cirrhosis (Fig. 3A) this was observed between week 0 to 24 (*p* = 0.003). In a small subset of patients (*n* = 12), longitudinal measurements of liver stiffness via transient elastography (FibroScan) were available. In contrast to the FIB-4 decline, there was no significant effect, indicating stable liver stiffness in this subgroup (data not shown). In another subset of

patients, measurements of IgG were conducted (*n* = 15, Fig. 4). Cirrhosis was present in 10/15 patients. Mean baseline IgG (g/L) levels were elevated (21.7 \pm 5.5) and decreased within 12 (19.8 \pm 4.9, *p* = 0.001) and 24 weeks (18.1 \pm 4.3, *p* = 0.001) of treatment.

There was evidence of decompensated liver disease at treatment initiation in five patients. Four cases were classified as Child-Pugh B and one case as Child-Pugh C. These patients are of special interest as clinical trials excluded patients with decompensated cirrhosis. As shown in Fig. 5, all five patients showed a virologic response. All but one patient showed decreasing ALT levels and rising platelet counts. One patient with refractory ascites (shown in purple in Fig. 5) experienced a temporary improvement in ascites.

In total, bulevirtide treatment was stopped in 6/114 cases. We have no evidence of drug-related serious adverse events leading to the termination of bulevirtide. In one case, treatment was stopped after liver transplantation for pre-existing HCC. In one patient, bulevirtide treatment was stopped after an event of hepatic decompensation. The event was considered to be unrelated to bulevirtide treatment by the responsible physician. In one case, insufficient response led to the termination of bulevirtide. In a second case with hepatic decompensation and *de novo* development of ascites during treatment, bulevirtide was continued. In that case, ascites improved under continued bulevirtide treatment, leading to hepatic re-compensation. In

Table 3. Comparison of baseline characteristics depending on the viral response status at week 24.

Patient characteristics at baseline (n = 33)	Viral response at week 24 (n = 19)	Viral non-response at week 24 (n = 3)	Intermediate viral response at week 24 (n = 11)	Post hoc <i>p</i> value
ALT U/L, mean \pm SD	114 \pm 85	140 \pm 10	109 \pm 64	0.85*, 0.98**, 0.80***
Age, years \pm SD	49 \pm 8	36 \pm 9	47 \pm 16	0.20*, 0.93**, 0.32***
Cirrhosis, n	12/19	2/3	4/11	0.33 (overall group comparison)
Platelets $\times 10^3/\mu$ L, median	133	158	130	0.52*, 0.86**, 0.65***

*Response vs. non-response, **Response vs. intermediate response, ***Non-response vs. intermediate response.

Data were compared by univariate ANOVA followed by a Tukey *post hoc* test. A Pearson Chi-square test was used for the presence of cirrhosis. ALT, alanine aminotransferase.

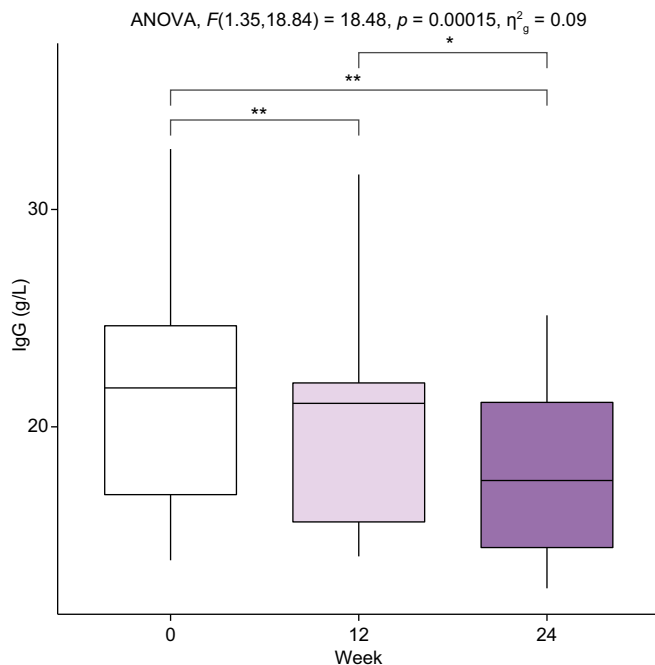


Fig. 4. IgG levels at week 0, 12 and 24 (n = 15). Boxplots show IgG levels in 15 patients. Data were analyzed using a repeated-measurement ANOVA and *post hoc* Bonferroni-corrected paired *t* test. * $p < 0.05$.

one case, the diagnosis of HCC was made under treatment and treatment was continued.

Discussion

Bulevirtide is the only approved treatment for hepatitis D. Herein, we report the first data from the largest multicenter real-world cohort of patients with hepatitis D treated with the

approved dose of 2 mg bulevirtide without additional PEG-IFNa. Our main findings were that (i) more than 50% of patients indeed achieve a virologic response (at least 2 log HDV RNA decline) with less than 10% of patients not achieving an HDV RNA drop of at least 1 log after 24 weeks; (ii) an improvement of biochemical hepatitis activity as measured by ALT values was seen regardless of virologic response status, and (iii) treatment was safe and well tolerated and prolonged treatment was associated with better clinical surrogate parameters of cirrhosis and portal hypertension.

Most patients showed an HDV RNA decline which was evident at 12 weeks of bulevirtide treatment and which continued throughout the ongoing therapy. Supposedly, bulevirtide does not interfere with the HDV life cycle in already infected cells but blocks HDV/HBV entry. Thus, not yet infected hepatocytes are protected by bulevirtide. A decline of HDV RNA during bulevirtide treatment should reflect a reduction of cells producing HDV RNA. This process takes some time, explaining why it may take several months to observe a profound HDV RNA decline in individual patients. Loss of HDV-infected cells has been demonstrated in bulevirtide-treated patients undergoing repeated liver biopsies in phase II and III trials.^{29,30} However, this process may differ between individuals and could be influenced by inter-individual variabilities in host immunity.³¹ On the other hand, HDV infection may be propagated by cell division which is not affected by bulevirtide. Whether cell-to-cell spread can explain a lack of virologic response in some patients remains to be investigated. We have to highlight that an increase in bile salts as a surrogate for an effective blocking of NTCP can be observed even in patients with a virologic non-response.³² Thus, *de novo* infection should be blocked in these patients and stable HDV RNA levels or even rebounds can only be explained by an increase in HDV-infected cells through other mechanisms.

In line with observations from previous trials and preliminary findings from other real-world cohorts,^{21,23,24} we also did not see a single patient with HBsAg loss during bulevirtide treatment. This is important as HDV RNA relapses after stopping bulevirtide

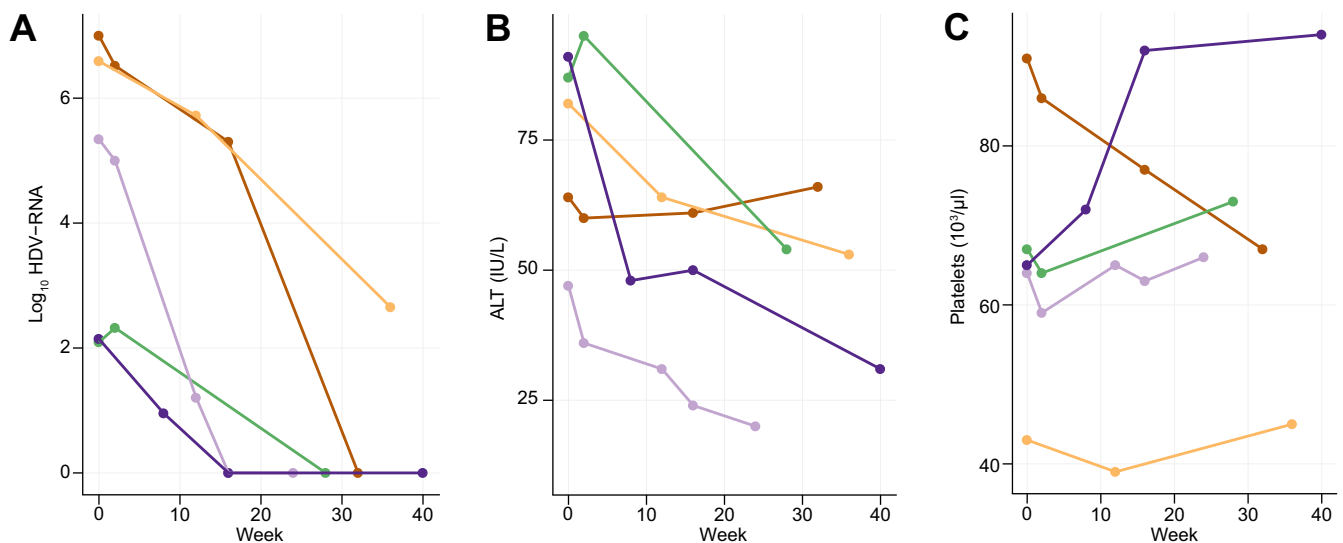


Fig. 5. Viral kinetics, ALT dynamics and platelet counts in patients with decompensated liver disease at treatment initiation (n = 5). Displayed are individual HDV RNA levels, ALT levels and the platelet count of five selected cases with evidence of decompensated liver disease at bulevirtide treatment initiation. ALT, alanine aminotransferase.

are likely in patients who do not lose HBsAg, even though a single case report – presented during a recent meeting – suggested that HDV cure may be possible in some patients after three years of bulevirtide monotherapy.³³

Importantly, a virologic response with HDV RNA declines translated into improvements of hepatitis activity in most patients. This is an important observation supporting the usefulness of the combined virologic and biochemical primary endpoint in clinical trials suggested by the FDA and EMA.³⁴ Interestingly, profound declines in ALT levels were also observed in some patients who were classified as virologic non-responders. Detailed mechanisms explaining this observation are currently lacking. One hypothesis is that an increase in bile salts may have anti-inflammatory effects on different immune cells.^{35,36} Moreover, NTCP blockade may protect hepatocytes from overload with bile salts and thereby confer hepatoprotective effects.³⁷ The improvement of hepatitis activity was thereby accompanied by a decline in IgG levels. Elevated IgG levels are commonly observed in autoimmune hepatitis. Features of autoimmunity have also been described in hepatitis D³⁸ and elevated IgG levels are frequently measured. The observed decline in IgG levels might therefore be a consequence of lowered hepatic inflammation and an additional response marker. Elevated IgG levels are also commonly observed in cirrhosis. As the majority of patients with available IgG measurements had cirrhosis, the observation of declining IgG levels might also be the consequence of reduced systemic inflammation due to improving cirrhosis and portal hypertension.

Importantly, bulevirtide treatment was safe in this real-world cohort and there were no apparent drug-related adverse events leading to treatment discontinuation. Two patients with compensated cirrhosis experienced an episode of hepatic decompensation during bulevirtide therapy. In one case, treatment was stopped. However, the event was considered to be unrelated to treatment. Treatment was continued in the other case, as the individual risk of a hepatitis flare caused by stopping bulevirtide treatment was considered too high. In fact, hepatic re-compensation occurred under continued bulevirtide treatment. In addition, we herein report data from five patients with initially decompensated liver disease who showed good virologic and biochemical response rates. This is the very first – even though anecdotal – evidence that bulevirtide may also safely be given to patients with decompensated cirrhosis. However, prospective trials are urgently needed to determine the role of bulevirtide in this vulnerable group of patients. More than 95% of patients were treated with NAs. While the coadministration of NAs is considered safe and has been practiced in clinical trials, certain drug-drug-interactions have to be considered. Based on *in vitro* tests, substances interfering with the NTCP-receptor (e.g. ciclosporin A, ritonavir, ezetimibe) are not recommended during bulevirtide treatment.³⁹

Interestingly, as a non-invasive marker of liver disease severity, FIB-4 improved over time. Beside the decrease in liver enzymes, the decline of FIB-4 is further substituted by the trend

of increasing platelet counts during treatment. This has also been observed in an Italian cohort of patients with advanced compensated cirrhosis treated with bulevirtide.²¹ In contrast, liver stiffness measurements did not reveal significant changes over time, however, data were available only for a small subgroup of patients. In order to adequately capture improvements in portal hypertension and cirrhosis, repeated invasive tests such as liver biopsies or hepatic venous pressure gradient measurements are of great interest. Overall, we would suggest that beyond HDV RNA declines and improvements in liver enzymes, there is evidence that prolonged bulevirtide treatment will translate into a reduction of clinical complications of liver disease in most patients with cirrhosis.

This study has obvious strengths and limitations. A large number of patients were treated in 16 centers outside of clinical trials. We estimate that more than 50% of patients treated with bulevirtide in Germany within the first 6 months after EMA approval were included in this analysis. Consequently, this report clearly reflects the true real-world setting of hepatitis D in Germany. It also needs to be highlighted that more than 50% of patients had cirrhosis, including 44% of patients with evidence of portal hypertension defined as the presence of esophageal varices or platelet counts below 100,000/ μ l. Thus, we demonstrate that bulevirtide is safe and effective in a cohort of patients with advanced compensated cirrhosis. Moreover, five cases with hepatic decompensation at treatment start were included.

However, we have to acknowledge that – given the nature of a retrospective analysis of real-world experience – data collection did not follow a standardized treatment protocol. Patient selection and management of patients with suboptimal virologic response may have differed between sites. There was also no centralized diagnostic virology laboratory, which precluded an analysis of absolute HDV RNA levels at distinct time points, only allowing for the investigation of relative HDV RNA declines. Several studies showed that there is large variation in HDV RNA quantification even between experienced diagnostic laboratories.^{40–42} Moreover, based on the nature of this retrospective collection of routine clinical data, not all data were available for all patients at all time points.

In summary, we herein report data on more than 100 patients with hepatitis D treated outside of clinical trials with a daily dose of 2 mg bulevirtide without additional PEG-IFNa. We confirm experiences from pivotal phase II and III trials and highlight that a subgroup of patients may not sufficiently respond in terms of HDV RNA decline or experience virologic relapse despite continued bulevirtide treatment. Alternative treatment strategies need to be developed for these patients.¹³ Future studies also need to explore if bulevirtide treatment could be stopped in some patients, which was not addressed here as almost all of our patients are still continuing bulevirtide therapy. Based on our experience, we suggest that bulevirtide is a safe and largely effective treatment option for patients with hepatitis D which can be offered to all patients with compensated liver disease.

Abbreviations

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; NTCP, sodium taurocholate cotransporting polypeptide.

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Conflict of interest

CD has received travel support from Gilead. FT has received grants or contracts from any entity from Allergan, BMS, Inventiva, Gilead; consulting fees from Allergan, Bayer, Gilead, BMS, Boehringer, Intercept, Ionis, Inventiva, Merz, Pfizer, Alnylam, NGM, CSL Behring, Novo Nordisk, Novartis; payment for expert testimony from Alnylam; support for attending meetings and/or travel from Gilead; participation on a Data Safety Monitoring Board or Advisory Board from Pfizer. CZ has no COI. MD has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead and MYR, support for attending meetings and/or travel from Gilead; participation on a Data Safety Monitoring Board or Advisory Board from Gilead and MYR. HS has no COI. CS received support for attending meetings and/or travel from Abbvie and Gilead, participation on a Data Safety Monitoring Board or Advisory Board from Gilead. KW has no COI. CL has received consulting fees from CSL Behring, Boston Scientific, Astra Zeneca, Eisai, Shionogi, Sobi; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Gilead, Falk, BSL Behring, Eisai; support for attending meetings and/or travel from Gilead and Abbvie. SW received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Falk and Abbvie; support for attending meetings and/or travel from Orphan, Falk, Abbvie. GD received consulting fees from Alexion, Gilead, Intercept, Novartis, Orphan, Univar; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Falk Foundation, Gilead, Intercept, Novartis, Orphan; support for attending meetings and/or travel support from Gilead and Intercept. CB received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead; and support for attending meetings and/or travel from Gilead. JG has no COI. UM received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from CSL Behring, MSD, Falk, Univar, Microbiotica; support for attending meetings and/or travel from Gilead; participation on a Data Safety Monitoring Board or Advisory Board from Takeda, Gilead, CSL Behring; AO has no COI; SZ reports speaker's bureau and/or consultancy for Abbvie, BioMarin, Gilead, GSK, Intercept, Janssen, Madrigal, MSD/Merck, NovoNordisk, SoBi and Theratechnologies, GSK, Gilead, Intercept; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, BioMarin, Janssen, MSD/Merck; payment for expert testimony and support for attending meetings and/or travel from Gilead. KS received grants from Gilead; honoraria for lectures from Gilead, Abbvie and MSD; support for attending meetings and/or travel from Gilead and Abbvie; participated in advisory boards from Gilead. TB received grants or contracts from any entity from Abbvie, BMS, Gilead, MSD/Merck, Humedics, Intercept, Merz, Novartis, Sequana Medical, received consulting fees from Abbvie, Alexion, Bayer, Gilead, Eisai, GSK, Intercept, Ipsen, Janssen, MSD/Merck, Novartis, Roche, Sequana Medical, and Shionogi; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Alexion, Bayer, Gilead, Eisai, Intercept, Ipsen, Janssen, MedUpdate GmbH, MSD/Merck, Novartis, and Sequana Medica; has received support for attending meetings and/or travel from Gilead, Abbvie, Intercept, Janssen. FB received grants or contracts from any entity from Gilead, Ipsen, Roche, Janssen; consulting fees from Gilead, Janssen, Astra Zeneca, MSD, Janssen, Advanz Pharma; support for attending meetings and/or travel from Advanz Pharma and Gilead, reports participation on a Data Safety Monitoring Board or Advisory Board from Janssen. JW has no COI. TH received author honoraria from Falk. TS has no COI. EZ has no COI. ND has no COI. RT has no COI. CNH received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Gilead, GSK, MSD, Falk Foundation. PG has no COI. MS participated in advisory boards from Gilead. AL received consulting fees from Roche, reports participation in advisory boards from Roche, MSD and Genfit. JSW received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and travel support from Gilead. JK has no COI. AG received payment for expert testimony from AbbVie, Alexion, Bayer, BMS, Eisai, Gilead, Intercept, Ipsen, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, Sequana. FR received payment or honoraria for lectures, presentations, speakers

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

KD and HW designed the study and wrote the manuscript; CD conducted data analyses and wrote the manuscript; all co-authors were involved in the data collection and preparation of the manuscript.

Data availability statement

Data is available upon request.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2023.100686>.

References

Author names in bold designate shared co-first authorship

- [1] Rizzetto M, Hamid S, Negro F. The changing context of hepatitis D. *J Hepatol* 2021;74:1200–1211.
- [2] **Urban S, Neumann-Haefelin C**, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. *Gut* 2021;70:1782–1794.
- [3] Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol* 2020;73:523–532.
- [4] Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *The Lancet* 2011;378:73–85.
- [5] Kamal H, Westman G, Falconer K, Duberg AS, Weiland O, Haverinen S, et al. Long-term study of hepatitis delta virus infection at secondary care centers: the impact of viremia on liver-related outcomes. *Hepatology* 2020;72:1177–1190.
- [6] Calle Serrano B, Grosshennig A, Homs M, Heidrich B, Erhardt A, Deterding K, et al. Development and evaluation of a baseline-event-anticipation score for hepatitis delta. *J Viral Hepat* 2014;21:e154–e163.
- [7] Alfaiate D, Clément S, Gomes D, **Goossens N, Negro F**. Chronic hepatitis D and hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. *J Hepatol* 2020;73:533–539.

- [8] Rizzetto M, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut* 1977;18:997–1003.
- [9] Wang KS, Choo QL, Weiner AJ, Ou JH, Najarian RC, Thayer RM, et al. Structure, sequence and expression of the hepatitis delta (delta) viral genome. *Nature* 1986;323:508–514.
- [10] Weiner AJ, Choo QL, Wang KS, Govindarajan S, Redeker AG, Gerin JL, et al. A single antigenomic open reading frame of the hepatitis delta virus encodes the epitope(s) of both hepatitis delta antigen polypeptides p24 delta and p27 delta. *J Virol* 1988;62:594–599.
- [11] Sheu GT. Initiation of hepatitis delta virus (HDV) replication: HDV RNA encoding the large delta antigen cannot replicate. *J Gen Virol* 2002;83:2507–2513.
- [12] Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. *eLife* 2012;1.
- [13] Sandmann L, Wedemeyer H. New treatments for chronic hepatitis B virus/hepatitis D virus infection. *Clin Liver Dis* 2021;25:831–839.
- [14] Sandmann L, Wedemeyer H. Interferon-based treatment of chronic hepatitis D. *Liver Int* 2022;00:1–11.
- [15] Wranke A, Serrano BC, Heidrich B, Kirschner J, Bremer B, Lehmann P, et al. Antiviral treatment and liver-related complications in hepatitis delta. *Hepatology* 2017;65:414–425.
- [16] Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2009;136:1629–1638.
- [17] Scheller L, Hilgard G, Anastasiou O, Dittmer U, Kahraman A, Wedemeyer H, et al. Poor clinical and virological outcome of nucleos(t)ide analogue monotherapy in HBV/HDV co-infected patients. *Medicine (Baltimore)* 2021;100:e26571.
- [18] Bockmann JH, Grube M, Hamed V, von Felden J, Landahl J, Wehmeyer M, et al. High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort. *BMC Gastroenterol* 2020;20:24.
- [19] Wranke A, Hardtke S, Heidrich B, Dalekos G, Yalçın K, Tabak F, et al. Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta. *J Viral Hepat* 2020;27:1359–1368.
- [20] Wedemeyer H, Schöneweis K, Bogomolov P, Blank A, Voronkova N, Stepanova T, et al. Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial. *Lancet Infect Dis* 2023 Jan;23(1):117–129.
- [21] Loglio A, Ferenci P, Uceda Renteria SC, Tham CYL, Scholtes C, Holzmann H, et al. Safety and effectiveness of up to 3 years' bulevirtide monotherapy in patients with HDV-related cirrhosis. *J Hepatol* 2022;76:464–469.
- [22] Loureiro D, Castelnau C, Tout I, Boyer N, Narguet S, Menasria Benazzouz S, et al. New therapies for hepatitis delta virus infection. *Liver Int* 2021;41(Suppl 1):30–37.
- [23] Jachs M, Schwarz C, Panzer M, Binter T, Aberle SW, Hartl L, et al. Response-guided long-term treatment of chronic hepatitis D patients with bulevirtide—results of a “real world” study. *Aliment Pharmacol Ther* 2022;56:144–154.
- [24] Herta T, Hahn M, Maier M, Fischer J, Niemeyer J, Hönemann M, et al. Efficacy and safety of bulevirtide plus tenofovir disoproxil fumarate in real-world patients with chronic hepatitis B and D Co-infection. *Pathogens* 2022;11.
- [25] Zöllner C, Hofmann J, Lutz K, Tacke F, Demir M. Real-life experiences with bulevirtide for the treatment of hepatitis delta—48 weeks data from a German centre. *Liver Int* 2022 Nov;42(11):2403–2407.
- [26] Lampertico P, Roulot D, Wedemeyer H. Bulevirtide with or without pegIFNα for patients with compensated chronic hepatitis delta: from clinical trials to real-world studies. *J Hepatol* 2022 Nov;77(5):1422–1430.
- [27] Team RCR. A language and environment for statistical computing. R Foundation for Statistical Computing; 2020.
- [28] Kassambara A. Rstatix: pipe-friendly framework for basic statistical tests. 2021.
- [29] Allweiss L, Volz T, Wedemeyer H, Schöneweis K, Alexandrov A, Bockmann J, et al. Analysis of liver biopsies reveals a strong intrahepatic reduction of HDV and inflammatory markers after treatment with Myrcludex B in combination with Tenofovir in chronic HBV/HDV infected patients. *Z Gastroenterol* 2019;57(1):e6–e7.
- [30] Allweiss L, Volmari A, Ladiges Y, Eggers C, Giersch K, Schöneweis K, et al. Strong intrahepatic decline of hepatitis D virus RNA and antigen after 48 weeks of treatment with bulevirtide in chronic HDB/HDV co-infected patients: interim results from a multicenter, open-label, randomized phase 3 clinical trial (MYR301). *Hepatology* 2021;74:1–56.
- [31] Kefalakes H, Horgan XJ, Jung MK, Amanakis G, Kapuria D, Bolte FJ, et al. Liver-resident bystander CD8(+) T cells contribute to liver disease pathogenesis in chronic hepatitis D virus infection. *Gastroenterology* 2021;161:1567–1583.e1569.
- [32] Deterding K, Xu C, Port K, Maasoumy B, Cornberg M, Wedemeyer H. Baseline bile acid levels but not bile acid increases during bulevirtide treatment of hepatitis D are associated with HDV RNA decline. *J Hepatol* 2022;77:S857.
- [33] Anolli M, Degasperis E, Uceda Renteria C, Sambarino D, Borghi M, Perbellini R, et al. Off-therapy cure of hepatitis delta after 3 years of bulevirtide monotherapy in a patient with compensated advanced cirrhosis. *J Hepatol* 2022;77.
- [34] Food and drug administration (FDA). Chronic hepatitis D virus infection: developing drugs for treatment guidance for industry. 2019.
- [35] Calmus Y, Poupon R. Shaping macrophages function and innate immunity by bile acids: mechanisms and implication in cholestatic liver diseases. *Clin Res Hepatol Gastroenterol* 2014;38:550–556.
- [36] Chang S, Kim YH, Kim YJ, Kim YW, Moon S, Lee YY, et al. Taurodeoxycholate increases the number of myeloid-derived suppressor cells that ameliorate sepsis in mice. *Front Immunol* 2018;9:1984.
- [37] Slijepcevic D, Roscam Abbing RLP, Fuchs CD, Haazen LCM, Beuers U, Trauner M, et al. Na(+) -taurocholate cotransporting polypeptide inhibition has hepatoprotective effects in cholestasis in mice. *Hepatology* 2018;68:1057–1069.
- [38] Strassburg CP, Obermayer-Straub P, Manns MP. Autoimmunity in hepatitis C and D virus infection. *J Viral Hepat* 1996;3:49–59.
- [39] Hepcludex epar product information. cited; Available from: https://www.ema.europa.eu/en/documents/product-information/hepcludex-epar-product-information_de.pdf.
- [40] Le Gal F, Brichler S, Sahli R, Chevret S, Gordien E. First international external quality assessment for hepatitis delta virus RNA quantification in plasma. *Hepatology* 2016;64:1483–1494.
- [41] Bremer B, Anastasiou OE, Ciesek S, Wedemeyer H. Automated nucleic acid isolation methods for HDV viral load quantification can lead to viral load underestimation. *Antivir Ther* 2019;24:117–123.
- [42] Stelzl E, Ciesek S, Cornberg M, Maasoumy B, Heim A, Chudy M, et al. Reliable quantification of plasma HDV RNA is of paramount importance for treatment monitoring: a European multicenter study. *J Clin Virol* 2021;142:104932.