Review

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Bulevirtide with or without pegIFNα for patients with compensated chronic hepatitis delta: From clinical trials to real-world studies

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Summary

Chronic hepatitis D (CHD) is the most severe form of viral hepatitis, characterised by the greatest increase in risk of cirrhosis, hepatic decompensation and hepatocellular carcinoma. Pegylated-interferon-α (pegIFNα), the only off-label therapeutic option, has been available for the last 30 years but is associated with suboptimal response rates and poor tolerability. Among the new treatment strategies under clinical evaluation, the entry inhibitor bulevirtide (BLV) is the only one that has received conditional approval from the European Medicines Agency (EMA); approval was granted in July 2020 for the treatment of adult patients with compensated CHD at a dose of 2 mg daily. Phase II studies and the week 24 interim analysis of a phase III study demonstrated the efficacy and safety of this treatment as a monotherapy or combined with pegIFNα. This favourable profile has been confirmed by recent real-world studies performed in Europe. As a long-term monotherapy, BLV has been successfully used to treat patients with advanced compensated cirrhosis. These encouraging yet preliminary findings must be viewed with caution as many critical issues related to this new antiviral strategy are still poorly understood, as summarised in this review. While waiting for new anti-HBV and anti-HDV drugs to become available for combination studies, BLV treatment is currently the only available anti-HDV therapeutic option that might improve the long-term prognosis of difficult-to-manage patients with CHD.

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Introduction

It is currently estimated that HDV infects between 10 and 20 million individuals worldwide.[1] Chronic hepatitis D (CHD) resulting from HDV infection presents as the most severe form of viral hepatitis, and is characterised by an increased risk of cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC).

HDV is a defective RNA virus that requires the hepatitis B surface antigen (HBsAg) to enter liver cells and then disseminate. The HDV replication cycle is not affected by conventional antiviral therapies such as the viral polymerase inhibitors used in HBV infection. For a long time, treatment with pegylated-interferon-α (pegIFNα) was the only available therapeutic option despite weak response rates[2] and poor tolerance. Moreover, a large proportion of responding patients relapsed, even several years after the end of treatment, leading to the need for repetitive long-term evaluation of HDV RNA viral load.[3,4]

New molecular targets have recently been identified, leading to the development of new drugs directed against HDV.[5] Some compounds, prescribed as monotherapy or in combination with pegIFNα have been evaluated in clinical trials.[5] Among them, the peptide entry-inhibitor bulevirtide (BLV) previously known as myrcludex B blocks the binding of HBsAg-enveloped particles to the NTCP (sodium taurocholate co-transporting polypeptide), which is the cell entry receptor for both HBV and HDV. It thus prevents the entry of HDV into hepatocytes and subsequent spreading of the virus.[6] The favourable therapeutic potential and the good tolerability of BLV were reported in a phase II trial,[7] while a phase III trial is ongoing. As a consequence, BLV received conditional approval from the European Medicines Agency (EMA) in July 2020, at the dose of 2 mg daily, for the treatment of adult patients with compensated CHD (*European Medicines Agency* https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex).

The approval decision mentioned that BLV should be continued in case of clinical benefits. However, the criteria defining clinical benefit and the optimal duration of BLV treatment have not been determined.

In the present article, we will review the efficacy and safety data on BLV, prescribed alone or in combination with pegIFNα in clinical trials and in "real-world" studies, and propose adapted therapeutic strategies according to liver disease severity.

Clinical trials

MYR202 study

In the multicentre phase II MYR202 study,[8] 120 tenofovir disoproxil fumarate (TDF)-treated patients with CHD were randomised to different BLV doses (2, 5, or 10 mg/day) or TDF monotherapy for

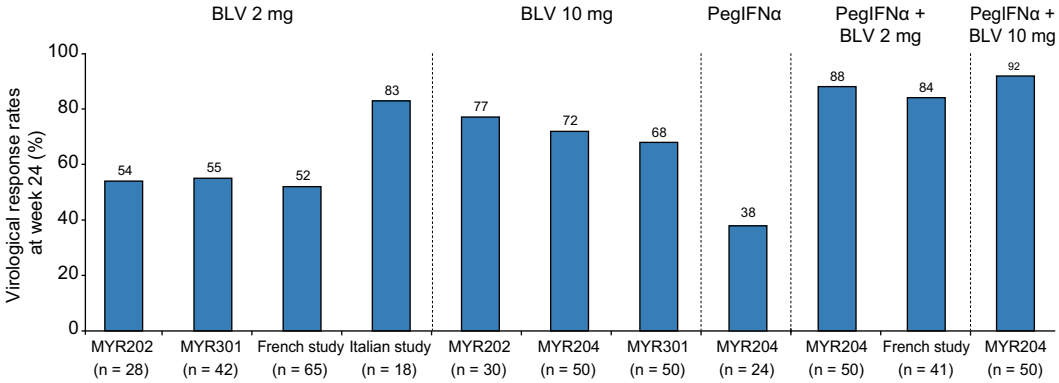

Fig. 1. Virological response rates at week 24 during treatment in patients treated with BLV 2 or 10 mg ± pegIFNα or pegIFNα monotherapy. Virological response rate defined as proportion of patients achieving undetectable HDV RNA or ≥2 log IU/ml decline *vs.* baseline. BLV, bulevirtide; pegIFNα, pegylated-interferon-α.

24 weeks followed by a period of TDF alone for 24 weeks for BLV-containing arms as well as for the control group (overall a 48-week study). About half of the patients had compensated cirrhosis (Table S1). The primary endpoint of the study, a 2-log decline or undetectable HDV RNA at week 24, was reached by 54%, 50% and 77% of the patients treated with increasing doses of BLV but only in 3% of those on TDF monotherapy (Fig. 1). Alanine aminotransferase (ALT) normalised in 43%, 50%, 40%, and 6% of patients on 2, 5, or 10 mg/day of BLV or TDF monotherapy, respectively, while a combined response (≥2 log decline from baseline or HDV RNA undetectable and normalisation of ALT levels) was achieved by 21%, 28%, 37% and 0% of patients, respectively (p <0.05 for all BLV groups *vs.* TDF). A dose-dependent decline of HDV RNA and ALT levels was observed. HBsAg levels were not affected by BLV therapy. At week 48, an HDV RNA relapse occurred in 60%, 80% and 83% of end of treatment HDV RNA responders in the BLV 2, 5, and 10 mg/day treatment arms and was associated with a moderate increase in ALT levels.

MYR203 study

In the phase II MYR203 study,[9] treatment with BLV, at different doses and with or without pegIFNα, was extended to 48 weeks. Ninety patients with chronic HBV/HDV co-infection were randomised into 6 treatment arms: pegIFNα 180 μg QW, 2 mg BLV+pegIFNα, 5 mg BLV+pegIFNα, 2 mg BLV, 10 mg BLV+pegIFNα and 10 mg BLV+TDF. In contrast to the MYR202 study, a nucleos(t)ide analogue backbone was not included in the first 5 treatment arms (Table S1). The primary efficacy endpoint, HDV RNA below the lower limit of detection (10 IU/ml) at week 72 (24 weeks off-therapy), was achieved by 0%, 53.3%, 26.7%, 6.7%, 6.7% and 33.3% of patients randomised to pegIFNα 180 μg QW, 2 mg BLV+pegIFNα, 5 mg BLV+pegIFNα, 2 mg BLV, 10 mg BLV+pegIFNα and 10 mg BLV+TDF, respectively. The corresponding ALT normalisation rates were 10%, 58.8%, 33.3%, 23.1%, 35.7% and 35.7%. HBsAg response defined as HBsAg loss or >1 log IU/ml decline at week 72 was observed only in patients treated with BLV combined with pegIFNα: 40% (6 of 15 patients) for BLV 2 mg, 13.3% (2 of 15 patients)

Key point

Approximately 10-20 million patients are co-infected with HBV and HDV. CHD is the most severe form of chronic viral hepatitis, which is characterised by fast progression to cirrhosis, decompensation and HCC.

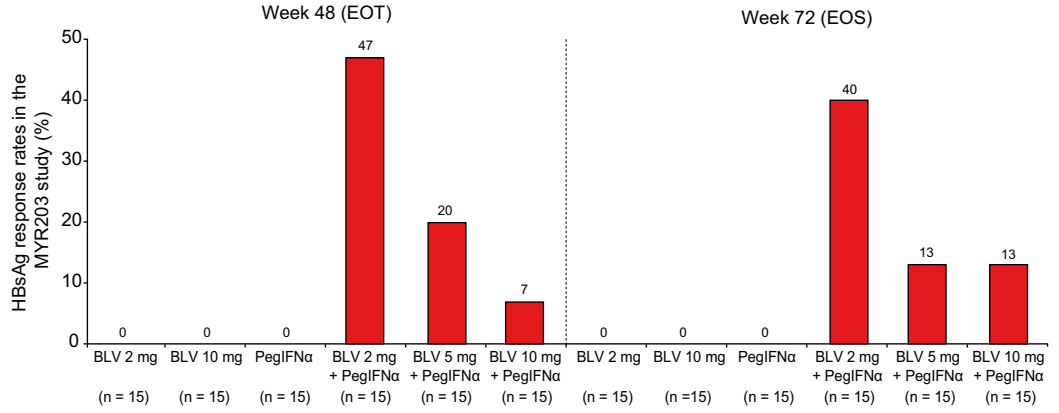

Fig. 2. HBsAg response, defined as the proportion of patients achieving HBsAg loss or >1 log IU/ml decline *vs.* baseline, during and off therapy in the MYR203 study. BLV, bulevirtide; EOS, end of study; EOT, end of treatment; HBsAg, hepatitis B surface antigen; pegIFNα, pegylated-interferon-α.

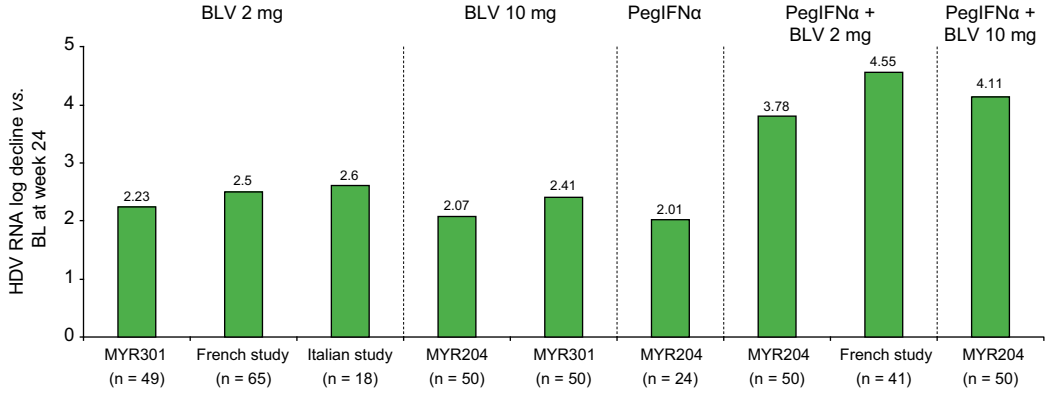

Fig. 3. HDV RNA log decline at week 24 *vs.* baseline in patients treated with BLV 2 or 10 mg ± pegIFNα or pegIFNα monotherapy. BLV, bulevirtide; pegIFNα, pegylated-interferon-α.

for BLV 5 mg, and 13.3% (2 of 15 patients) for BLV 10 mg (Fig. 2). HBsAg loss occurred in 4 (27%) and 1 (7%) patient(s) treated with BLV 2 mg or 10 mg plus pegIFNα, respectively. Combination therapy with pegIFNα showed strong synergism with respect to HDV RNA decline on treatment, but off-treatment HDV RNA responses at week 72 were only observed in patients achieving an HBsAg response.

Key point

In the last 30 years, the only available antiviral therapy has been based on the off-label use of IFNα or pegIFNα. However, this strategy is suboptimal due to the limited durability of virological responses and significant side effects.

MYR204 study

In this phase IIb study, 175 patients with compensated CHD were randomised to 4 arms: 180 μg/week of pegIFNα monotherapy for 48 weeks with a post-treatment follow-up of 48 weeks; 180 μg/week of pegIFNα plus 2 mg/day BLV for 48 weeks, followed by 48 weeks of BLV 2 mg monotherapy; 180 μg/week of pegIFNα plus 10 mg/day BLV for 48 weeks, followed by 48 weeks of BLV 10 mg/day monotherapy and BLV 10 mg/day monotherapy for 96 weeks with a post-treatment follow-up of 48 weeks for the 3 last arms[10] (Table S1). The primary endpoint of this ongoing study will be HDV RNA undetectable (<limit of detection) at week 24 after end of treatment. The combination of BLV with pegIFNα resulted in a more profound decline of HDV RNA, independently of the BLV dose, compared to either monotherapy: 3.78 (for 2 mg BLV±pegIFNα) and 4.11 (for 10 mg BLV+pegIFNα) median log IU/ml decline compared to 2.01 for pegIFNα monotherapy and 2.07 for BLV 10 mg monotherapy (Fig. 3). Likewise, the proportion of patients with HDV RNA decline ≥2 log IU/ml from baseline was 38%, 88%, 92% and 72.0% and undetectable viremia was 13%, 24%, 34% and 4% in the pegIFNα monotherapy, 2 mg BLV+pegIFNα, 10 mg BLV+pegIFNα, and BLV 10 mg monotherapy arms, respectively (Figs. 1 and 4). In contrast, biochemical response, defined as ALT normalisation, was more favourable in patients treated with BLV 10 mg monotherapy (64%) than in those treated with pegIFNα monotherapy (13%) or pegIFNα combined with BLV 2 mg (30%) or BLV 10 mg (24%) (Fig. 5). 50% of the patients in the BLV 10 mg group compared to 13% in the pegIFNα group and 30-24% in the pegIFNα plus BLV group achieved a combined response (Fig. 6). Combination therapy and BLV 10 mg monotherapy resulted in high rates of HDV RNA decline while BLV alone resulted in the highest rate of ALT normalisation. More than 1 log IU/ml decline of HBsAg levels *vs.* baseline was achieved only in the combination group (12% with BLV 2 mg and 8% with BLV 10 mg) and in the pegIFNα monotherapy group (4%). The week 48 efficacy and safety data will be presented at The International Liver Congress™ (ILC) 2022.

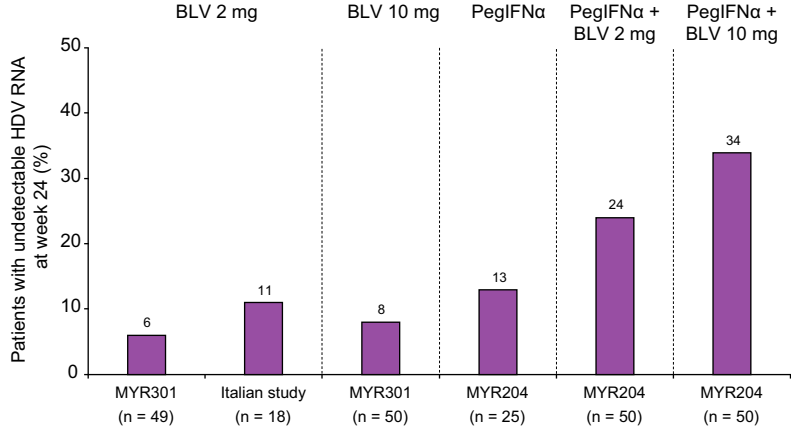

Fig. 4. Proportion of patients achieving undetectable HDV RNA at week 24 during treatment with BLV 2 or 10 mg ± pegIFNα or pegIFNα monotherapy. BLV, bulevirtide; pegIFNα, pegylated-interferon-α.

MYR301 study

In this ongoing phase III registration study for BLV,[11] 150 patients with chronic HBV/HDV co-infection were randomised to 3 different arms (Table S1): control group (48 weeks no treatment followed by 96 weeks 10 mg BLV), 2 mg BLV group (144 weeks of 2 mg BLV followed by 96 weeks of off-treatment follow-up); 10 mg BLV group (144 weeks of 10 mg BLV followed by 96 weeks of off-treatment follow-up). The primary objective is to

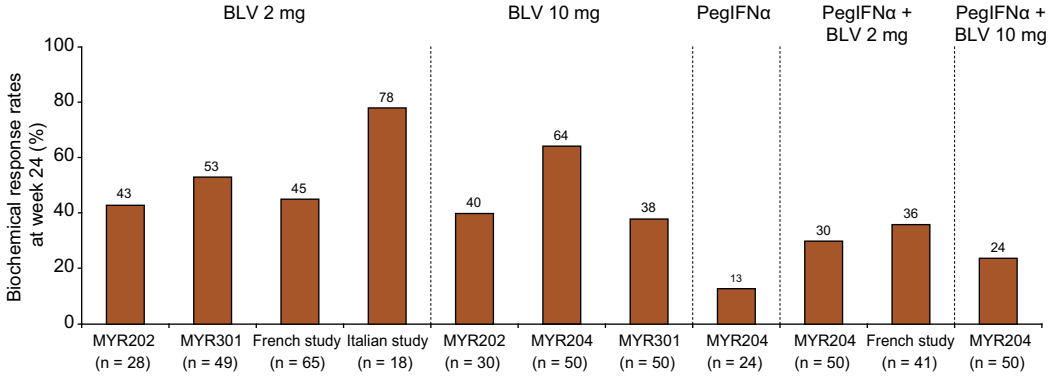

Fig. 5. Biochemical response rate at week 24 in patients treated with BLV 2 or 10 mg ± pegIFNα or pegIFNα monotherapy. Biochemical response rate defined as proportion of patients in whom ALT normalised. ALT, alanine aminotransferase; BLV, bulevirtide; pegIFNα, pegylated-interferon-α.

evaluate the safety and efficacy of different doses of BLV monotherapy administered for up to 144 weeks. The total duration of the study is 240 weeks. The primary endpoint of the study was the combined response rates at week 48. While the proportion of patients who achieved a virological response (HDV RNA decline ≥2 log IU/ml) at week 24 was 4%, 55% and 68%, respectively, only 0%, 6% and 8% achieved undetectable HDV RNA, *i.e.* <6 IU/ml (Figs. 1 and 4). HDV RNA declines of 0.079, 2.2 and 2.4 log IU/ml were observed in the 3 groups (Fig. 3). The ALT normalisation rates increased from 6% in the control group to 53% and 38% in the active drug groups (6% *vs.* 53%, p <0.0001; 6 *vs.* 38%, p <0001) (Fig. 5). The corresponding rates of combined responses were 0%, 37% (p <0.001 *vs.* control) and 28% (p <0.001 *vs.* control) (Fig. 6). Thus, 24 weeks of monotherapy with BLV 2 or 10 mg was associated with significant HDV RNA declines and improvements in biochemical disease activity but there was no clear dose effect observed in this trial. Similar to the MYR202 study, BLV monotherapy did not affect HBsAg levels. BLV monotherapy was well tolerated in patients with chronic HDV infection, with most adverse events (AEs) being mild-to-moderate and no BLV-related serious AEs. The week 48 efficacy and safety data will be presented at ILC 2022.

Patient-reported outcomes (PROs)

Patient-reported outcomes (Hepatitis Quality of Life Questionnaire [HQLQTM], including SF-36 and 15 supplementary items) were assessed in patients enrolled in the MYR301 study.[12] From baseline to week 24, BLV 2 mg-treated patients reported improvements in all domains on the HQLQTM, notably >5-point improvements in general health, bodily pain, vitality, mental health, hepatitis-specific (HS) limitations, and HS health distress and >4 points in social functioning and role functioning of emotional domains. Of note, untreated patients also reported >5-point improvements in mental health and HS health distress and >4-points on HS limitations. These interesting preliminary results require confirmation over 48 weeks; it will be particularly important to determine to what extent BLV improves quality of life compared to the untreated control group.

Intrahepatic virological response

The antiviral efficacy of BLV treatment was investigated using paired liver biopsies obtained at baseline and at week 48 from patients in the phase III clinical trial MYR301.[13] Paired liver biopsies from 79 patients (27 in the untreated control group, 21 in the BLV 2 mg group and 31 in the BLV 10 mg group) were used for HDV antigen (HDAg) staining (n = 79) and molecular analyses (n = 66). Virological parameters were assessed by qPCR and immunohistochemistry, expression of infection-related host genes was determined by qPCR. At week 48, intrahepatic HDV RNA strongly declined with median reductions from baseline of 2.2 log IU/ml in the BLV 2 mg group (n = 21) and 2.5 log IU/ml in the BLV 10 mg group (n = 27), leading to undetectable HDV RNA (lower limit of detection = 0.0001 relative expression) in 33% and 52% of the cases, respectively. Intrahepatic HDV RNA levels did not change in the untreated group. The number of HDAg+ cells significantly decreased both in the BLV 2 mg (median -2.1 Δ log) and BLV 10 mg (median -2.0 Δ log) groups, which strongly correlated with the decrease determined by qPCR (Spearman r = 0.94), but not in the control group. Transcriptional levels of several inflammatory chemokines (*e.g.* CXCL10 median -0.9 Δlog10) and interferon-stimulated genes (*e.g.* ISG15 median -0.3Log10) concomitantly decreased in BLV-treated patients. Importantly, these reductions strongly correlated with HDV RNA declines (*e.g.* CXCL10 *vs.* HDV RNA: r = 0.80), suggesting that HDV replication is the main driver of intrahepatic inflammation and ISG induction. By contrast and interestingly, BLV treatment did not reduce

Key point

In 2020, the EMA provisionally approved the first anti-HDV drug bulevirtide at the dose of 2 mg as daily self-administered subcutaneous injections. This is a first-in-class entry inhibitor that blocks NTCP-mediated intrahepatic spreading of HDV.

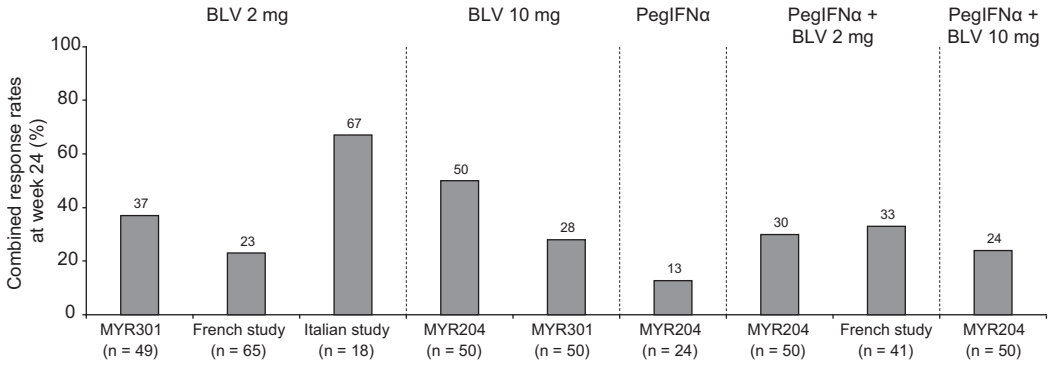

Fig. 6. Combined response rates at week 24 in patients treated with BLV 2 or 10 mg ± pegIFNα or pegIFNα monotherapy. Combined response rates defined as proportion of patients achieving an undetectable HDV RNA or ≥2 log IU/ml decline *vs.* baseline in whom ALT normalised. ALT, alanine aminotransferase; BLV, bulevirtide; pegIFNα, pegylated-interferon-α.

Key point

Clinical trials and real-world experiences demonstrated that bulevirtide 2 mg administered for 24 or 48 weeks as monotherapy or combined with pegIFNα reduces HDV viremia and normalises ALT levels in a significant proportion of patients. The combination of bulevirtide and pegIFNα shows a synergistic on-treatment effect compared to either monotherapy – however, a durable response is seen only in patients who lose HBsAg.

Key point

Treatment is generally well tolerated; an asymptomatic increase of bile acids has been noted.

intrahepatic HBV RNA or DNA levels, further confirming that BLV does not influence long-term infected cells. In this context it has to be noted that most patients in the MYR301 study received nucleos(t)ide analogue treatment for HBV.

Antiviral resistance analysis

In the MYR204 trial, 5/150 patients treated with BLV were classified as virological non responders (less than 1 log IU/ml decline of HDV RNA compared to baseline within 24 weeks of treatment), while in the MYR301 trial 15/100 patients met this classification.[14] Samples were available for resistance testing in 3/5 and 13/15 patients. An in-house virus stock, produced by Huh7-END cells, served as a control with a median EC50 of 0.18 nM (range 0.07-0.20). Median baseline EC50 values of responders and non-responders-were 0.16 nM (range 0.01-2.02) and 0.13 nM (range 0.05-0.61), respectively. The response to BLV *in vitro* was not any different at week 24 in non-responders, as they had a median EC50 value of 0.09 nM (range 0.02-1.32). The plasma concentration of BLV in patients treated with 2 mg daily for 14 weeks reached 4.4 nM on average and peaked at 25.8 nM, exceeding the *in vitro* measured EC50 range by 2-7-fold. In conclusion, these results indicate that the rarely observed cases of virological non-response at week 24 in the 2 studies were not associated with the development of resistant HDV and may therefore be explained by other host factors.

Real-world studies

The results of real-world studies from France, Italy, Austria, and Germany have recently been reported.

The French experience

In the French early access programme study, 133 patients received either BLV 2 mg/day monotherapy (n = 77) or BLV 2 mg/day combined with PegIFNα 180 μg/week (n = 56).[15] Patients were males (70%), mean age 41 years with advanced fibrosis or cirrhosis (64%). By per protocol analysis, HDV RNA declines from baseline to month 3, 6 and 12 were: -1.48, -2.50 and -3.64 log IU/ml in the BLV group; -3.24, -4.55, -5.55 log IU/ml in the combined group (Fig. 3). The virological response rates (undetectable HDV RNA or ≥2 log IU/ml decrease from baseline) in the 2 groups were 52% *vs.* 84% at week 24 and 68% *vs.* 94% at week 48, respectively (Fig. 1 and Fig. S1). The proportion of patients with undetectable HDV RNA at week 48 were 39% and 85%, respectively. The corresponding rates of ALT normalisation were 45% *vs.* 36% and 49% *vs.* 36% (Fig. 5). Overall, BLV was well tolerated with mild side-effects (headache, asthenia) and no discontinuations due to AEs; an asymptomatic increase of bile acids was observed in 99% and 100% of patients. In this first real-world cohort, daily BLV 2 mg monotherapy or combined with pegIFNα was well-tolerated over 12 months. Strong antiviral responses against HDV in the real-world setting confirmed previous trial results.

The early virological responses in 6 patients with CHD treated either with BLV 2 mg plus pegIFNα (n = 4) or BLV 2 mg monotherapy (n = 2) have recently been reported.[16] Four patients treated with combined therapy had a decline of a minimum of 1 log and 3/3 of 2 log IU/ml HDV RNA at 12 and 24 weeks, respectively. In 1 patient who had to stop treatment at 12 weeks because of thrombocytopenia, a virological relapse was noticed 24 weeks after treatment cessation. Three out of 4 patients had undetectable viremia (<100 copies/ml) during treatment. One patient (1/2) treated with BLV monotherapy had a decline of viremia by 1 log at 8 weeks and 1/1 by 2 logs at 28 weeks on-treatment. ALT normalised in 2/4 patients on combined therapy at 4 and 56 weeks. One patient (1/2) receiving BLV monotherapy achieved ALT normalisation at 4 weeks on treatment. HBsAg levels remained unchanged. Three out of 6 patients had an elevation of total bile acids without pruritus.

The Italian experience

Eighteen patients with compensated HDV-related cirrhosis and clinically significant portal hypertension and or active HCC were enrolled in a single-centre prospective cohort study.[17] A 24-week treatment with BLV 2 mg/day led to a 2.6 log IU/ml HDV RNA decline, with 83% of patients achieving a virological response defined as undetectable HDV RNA or ≥2 log IU/ml decline *vs.* baseline (Figs. 1, 3, 4). Virological non-response (defined as less than 1 log IU/ml decline at week 24 compared to baseline) was observed in 11%; ALT levels normalised in 78% of patients and 67% achieved a combined response, respectively (Figs. 5 and 6). No significant changes in HBsAg levels were observed. Platelet count and liver stiffness values remained unchanged during the first 24 weeks of therapy, but alpha-fetoprotein and IgG levels normalised. BLV was well tolerated even in these-difficult-to treat patients. An asymptomatic increase of bile acids was observed.

The Austrian experience

Fifteen patients (age 50.2 years; 9 with compensated cirrhosis) received BLV (2 mg/day in 12; 10 mg/day in 2), 14 as initial monotherapy.[18] During BLV monotherapy, 13/14 had at least a 1 log HDV RNA decline, including 3 with undetectable HDV RNA (<100 copies/ml) and 1 with a decrease to the lower limit of quantification. BLV treatment was terminated as planned in 2 patients with undetectable HDV RNA for >6 months. One non-cirrhotic patient received BLV 10 mg/day for 108 weeks, tapered to 5 mg/day and 2 mg/day, respectively, over the next 36 weeks. From week 96 on, HDV RNA was and remained undetectable 20 weeks after therapy. One other patient (with compensated cirrhosis) received 2 mg/day BLV for 63 weeks; HDV RNA became detectable after 4 weeks and BLV was restarted. Two patients dropped out due to non-compliance after 8 and 24 weeks, respectively. Eleven patients are still on treatment (24 to 140 weeks of therapy). Two patients became negative (at weeks 90 and 128); 1 had a >4-log decline (currently week 40); 1 had a >3-log decline (week 30) and 4 a maximum decline of 1-log (week 40, 30, 32 and 24). ALT levels normalised in 11 (84.6%) patients. Of the 2 patients who stopped BLV treatment, 1 maintained off-treatment response while the second restarted BLV after a virological relapse. During BLV therapy, HBsAg levels did not change, and bile acid levels increased without pruritus.

The German experience

Eight patients with active hepatitis B/D coinfection, all on nucleos(t)ide analogue therapy, were treated with BLV 2 mg/day for 16 weeks.[19] One patient dropped out shortly after inclusion because of a newly diagnosed HCC. In the 7 remaining patients, mean HDV RNA levels dropped from 10,902,457 copies/ml to 3,740,569 copies/ml and ALT values from 78 U/L at baseline to 39 U/L at week 16. BLV was discontinued in 1 patient who showed no significant biochemical or viral response. No relevant side effects apart from an asymptomatic elevation of bile acids were observed.

Table 2. Current challenges to the use of BLV therapy in patients with CHD.

Endpoints	Available data[a]
Week 48 efficacy and safety data of the MYR204 study	Currently unknown*
Week 48 efficacy and safety data of the MYR301 study	Currently unknown*
Optimal dose as monotherapy (2 *vs.* 10 mg/daily)	Limited data**
Off-therapy added value of pegIFNα combination	Limited data
Optimal duration of BLV monotherapy	Limited data
Off-therapy sustained virological response	Currently unknown
Off therapy HBsAg response	Limited data
Efficacy of long-term monotherapy (>48 weeks)	Limited data
Long-term safety of elevated bile acids	Limited data
End-of-therapy histological response	Limited data
Long-term clinical response	Limited data
Predictors of on- or off-therapy response	Currently unknown
Rates of virological non-response or resistance	Limited data
Long-term real-world effectiveness and safety data	Limited data

BLV, bulevirtide; HBsAg, hepatitis B surface antigen; pegIFNα, pegylated-interferon-α.
[a]At the time of writing, March 2022.
*Data to be presented at the ILC 2022 meeting.
**No evidence of dose-related effect at week 24, but no data off therapy yet.

Long-term BLV monotherapy (>48 weeks)

Two patients with compensated HDV-related cirrhosis, 1 from Italy and 1 from Austria, received BLV monotherapy for 3 years.[20] ALT levels normalised before week 28 in both patients, with both achieving undetectable HDV RNA (<6 IU/ml by Robogene assay) before week 52. Biochemical and virological responses were maintained over 3 years of BLV administration without relapse or breakthrough, even after dose reduction of BLV from 10 to 5 and 2 mg/day. In the patient with compensated cirrhosis and clinically significant portal hypertension, oesophageal varices disappeared, histological/laboratory features of autoimmune hepatitis secondary to HDV infection resolved, alpha-fetoprotein levels normalised, and liver stiffness, platelets and albumin levels significantly improved. As far as safety is concerned, only an asymptomatic, dose-related increase of total bile acids was observed. Of note, no HDV-specific T-cell responses became detectable even after prolonged suppression of HDV RNA.

Key point

Preliminary real-world studies further support the favourable virological and biochemical response to bulevirtide 2 mg as long-term monotherapy even in patients with advanced compensated cirrhosis or combined with pegIFNα.

Safety data

Overall, BLV has been well tolerated in clinical trials and real-world studies. Safety data for BLV 2, 5 and 10 mg monotherapy for 24 weeks are reported in the MYR202 study and for BLV 2 and 10 mg monotherapy for 48 weeks in the MYR203 study. Drug-related serious AEs were not reported and AEs leading to early drug discontinuation were not

Table 1. Suggested treatment strategies according to disease severity and presence of contraindications to pegIFNα.

Disease severity*	Contraindications to pegIFNα ?	Treatment strategy
Moderate to severe CHD or compensated cirrhosis without oesophageal/gastric varices	No	BLV 2 mg + pegIFNα for 48 weeks or pegIFNα monotherapy for 48 weeks
	Yes	BLV 2 mg monotherapy**
Compensated cirrhosis with oesophageal/gastric varices	No/Yes	BLV 2 mg monotherapy**
Decompensated cirrhosis	No/Yes	No approved therapy***

BLV, bulevirtide; CHD, chronic hepatitis D; pegIFNα, pegylated-interferon-α.
*Moderate or severe CHD defined by fibrosis extent, *i.e.* F2 and F3 by liver biopsy or non-invasive methods, respectively.
**The optimal duration of therapy is presently unknown.
***Refer to a tertiary hepatological centre for inclusion in clinical trial and assessment for liver transplantation.

observed. Moderate AEs like fatigue, nausea, headache, dizziness, leukopenia and thrombocytopenia occurred in 5 to 8% of patients. Injection-site reactions were observed in 6% and 26% of patients treated with BLV 2 mg and 10 mg, respectively, in the MYR301 study. These reactions were generally mild and short lasting. A dose-related increase of total bile acids was reported in all studies, but these increases were not associated with symptoms. Bile acid levels returned to baseline values when BLV was stopped in the MYR203 study. HDV RNA relapses after BLV treatment were associated with a moderate increase in ALT levels without clinical consequences in the MYR202 study. A favourable safety profile was also observed in patients with advanced compensated cirrhosis treated with BLV 2 mg monotherapy.[17] In general, the combination with pegIFNα did not induce any side effects apart from those usually associated with pegIFNα administration. The proportion of patients experiencing any treatment-emergent grade 3 or 4 AEs was greater in patients treated with pegIFNα (either as monotherapy or in combination) than in those treated with BLV monotherapy in the MYR204 study.

Key point

While waiting for new anti-HBV and/or anti-HDV drugs to enter the market, bulevirtide is the only approved therapeutic option for patients with compensated CHD.

Antiviral strategies

Currently, BLV 2 mg is the only EMA-approved drug for HDV treatment. The optimal dose of BLV treatment, *e.g.* daily injections of 2 mg *vs.* 10 mg, is currently being explored in an ongoing phase III trial. Based on the preliminary week 24 and 48 efficacy and safety data on BLV treatment with or without pegIFNα and the synergistic effect of this combination, 3 strategies could be envisaged (Table 1). For patients who can be treated with pegIFNα, a "curative" strategy based on short-term (48-week) administration of daily subcutaneous injections of 2 mg BLV combined with pegIFNα 180 μg/week may result in HBsAg response and sustained off-therapy HDV RNA negativity in some patients. The second option would be a finite course of BLV monotherapy. Since few patients maintained an off-treatment response after 24 to 48 weeks of BLV monotherapy in the treatment trials as well as in some real-world patients, immune control of HDV infection may be possible. However, we currently lack evidence that treatment with an entry inhibitor restores HDV-specific immunity and predictors of off treatment response are currently unknown. The third strategy, *i.e.* long-term administration of BLV monotherapy, should at this stage be the strategy of choice for the majority of patients (Table 1). Indeed, the EMA BLV label suggests continuing treatment for as long as a clinical benefit is evident. In particular, long-term treatment seems to be the preferred treatment strategy for patients with cirrhosis and a high risk of progressive liver disease and post-treatment flares.

These indications should be interpreted with caution as many relevant issues related to these treatment strategies remain unclear (Table 2). The efficacy and safety data beyond week 24 are very limited, the rates of virological non-response are unclear, the off-therapy virological and biochemical response rates are not known, the optimal duration of BLV monotherapy has not been defined yet and most of the enrolled patients were Caucasian and infected with HDV genotype 1. Importantly, the clinical outcomes of patients achieving a significant HDV RNA decline, *i.e.* more than 2 log decline *vs.* baseline, but not undetectable viremia needs to be evaluated in the context of BLV treatment. Although this endpoint has previously been shown to be associated with improved survival in IFN-treated patients with CHD, we acknowledge that the robustness of this virological response has not been confirmed by other clinical studies. We also want to emphasise that the primary endpoint of trials does not only include a decline in viral load but also ALT normalisation. We believe that biochemical improvement is crucial and should translate into improved outcomes. Moreover, different trial endpoints may be useful for long-term therapies (maintenance treatment) *vs.* finite treatment approaches where sustained off-treatment HDV RNA suppression seems to be a reasonable target. Also, the BLV-induced increase of bile acids and its biological consequences need to be investigated in this context (Table 2). Last but not least, most studies have not been published in full yet.

There is an urgent need for additional research on HDV infection, not only to determine the optimal BLV treatment regimen but also to better understand basic mechanisms of disease progression in HDV-induced liver disease, virological

control and treatment response. Novel and reliable biomarkers are needed to individualise the management of HDV infection – with or without BLV.

Conclusions

Forty-five years after the discovery of HDV by Mario Rizzetto, the first anti-HDV therapy has conditionally been approved by the EMA (FDA approval pending). BLV, the first-in-class entry inhibitor, has been shown to reduce HDV replication and normalise ALT levels in a significant proportion of patients with compensated CHD, either as monotherapy or combined with pegIFNα, in the context of a favourable safety profile. Although many relevant issues related to this therapy remain to be clarified, we might be able to stop/reduce viral replication and disease activity. While waiting for new anti-HBV and anti-HDV drugs to become available, BLV treatment might improve the long-term prognosis of difficult-to-manage patients with CHD.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; BLV, bulevirtide; CHD, chronic hepatitis Delta; CXCL10; C-X-C motif chemokine ligand 10; EC50, half maximal effective concentration; EMA, European Medicines Agency; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDAg, hepatitis delta antigen; HQLQTM, Hepatitis Quality of life Questionnaire; HS, hepatitis-specific; ISG, interferon-stimulated genes; NCTP, sodium taurocholate co-transporting polypeptide; NR, non-responder; pegIFNα, pegylated-interferon-α; QOL, quality of life; QW, once weekly; TDF, tenofovir disoproxil fumarate.

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Conflict of interest

PL: advisor and speaker bureau for BMS, Roche, Gilead Sciences, GSK, MSD, Abbvie, Janssen, Arrowhead, Alnylam, Eiger, MYR Pharma, Antios, Aligos, Vir. DR: advisor and speaker for Gilead Sciences and Abbvie. HW: consulting: Abbott, AbbVie, Aligos, Arbutus, BMS, Boehringer Ingelheim, Dicerna, Gilead, JJ/Janssen-Cilag, MyrGmbH, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, VIR, ViiV; speaking honoraria: Abbott, AbbVie, BMS, Boehringer Ingelheim, Gilead, JJ/Janssen- Cilag, MyrGmbH, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV.

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

Authors' contributions

Concept and design, interpretation of the data, drafting the article and critical revision**:** Pietro Lampertico, Dominique Roulot, Heiner Wedemeyer. All authors approved the final version of the manuscript.

Supplementary data

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Author names in bold designate shared co-first authorship

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