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INVITED REVIEW

Bulevirtide-based treatment strategies for chronic hepatitis delta: A review

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Abstract

Chronic hepatitis Delta (CHD) is a rare and severe form of chronic viral hepatitis. Until recently, the only therapeutic approach has been the off-label use of a 48 weeks course of PegInterferon alpha (PegIFNα), that was characterized by suboptimal efficacy and burdened by significant side effects that limited treatment applicability in patients with advanced liver disease. In July 2020, European Medicines Agency (EMA) conditionally approved the entry inhibitor Bulevirtde (BLV) at the dose of 2 mg/day for the treatment of adult patients with compensated CHD. Efficacy and safety of BLV in CHD have been evaluated in clinical trials either as monotherapy or in combination with PegIFNα. These results were confirmed by real-life studies, which also evaluated long-term BLV monotherapy in patients with advanced compensated cirrhosis. Notwithstanding these promising results there are still several issues to be addressed, such as the optimal duration of the treatment, the rates of off-therapy responses, as well as the long-term clinical benefits. This review summarizes updated and current literature data about clinical trials and real-life studies with BLV monotherapy and/or in combination with PegIFNα.

KEYWORDS
bulevirtide, chronic delta hepatitis, cirrhosis, combined response, entry inhibitor, HDV, HDV-RNA, virological response

1 | INTRODUCTION

Chronic hepatitis Delta (CHD) represents the most severe and progressive form of chronic viral hepatitis, resulting in high risk of cirrhosis and its complications, such as hepatocellular carcinoma (HCC), portal hypertension and decompensated end-stage liver disease.[1–3] It is estimated that CHD affects approximately 10–20 million of patients worldwide, with a 5%–10% prevalence in Hepatitis B surface antigen (HBsAg) positive patients. Hepatitis Delta virus (HDV) is a defective RNA virus, needing the presence of HBsAg from hepatitis B virus (HBV) to enter hepatocytes, replicate and spread.[3]

Conventional HBV therapies, that is nucleos(t)ide analogues (NUC), have no effect on HDV viral cycle: until now, the only therapeutic approach has been off-label therapy with PegInterferon alpha (PegIFNα), a strategy characterized by suboptimal off-therapy response rates (20%–30%) and safety profile.[4] PegIFNα-induced side effects resulted in limited treatment eligibility and de facto prevented antiviral therapy in patients with advanced liver disease, who represented the most-in-need patient population at high risk of liver-related complications and mortality. Following the discovery of new virological targets, novel anti-HDV drugs were developed and evaluated in clinical trials.[5] Bulevirtide (BLV), the first-in-class HBV

entry inhibitor, is a lipopeptide mimicking the Na+−taurocholate transporting polypeptide (NTCP) receptor binding domain, which hinders Hepatitis Delta virus (HDV) and HBV entry in hepatocytes, resulting in blockage of the NTCP-mediated HDV spread.[5,6] In Phase 2 trials, BLV has showed favourable efficacy and safety profile, that were confirmed in the interim analysis of the Phase 3 trial still ongoing.[7–11] In July 2020, the European Medicines Agency conditionally approved BLV at the dose of 2 mg/day subcutaneously for the treatment of adult patients with compensated CHD. The aim of this review is to provide a comprehensive overview of the current clinical trials and real-life studies about safety and efficacy of BLV either as monotherapy or in combination with PegIFNα.

2 | BLV MONOTHERAPY

2.1 | Clinical trials

In the multicentre phase 2 **MYR202 study**, 120 CHD patients (50% with cirrhosis) on Tenofovir disoproxil fumarate (TDF)-based treatment were randomized to receive different BLV doses (2 mg vs. 5 mg vs. 10 mg/day) vs. TDF monotherapy for 24 weeks. A virological response, defined as ≥2 Log IU/ml decline or undetectable HDV RNA at Week 24, was achieved by 54% vs. 50% vs. 77% in BLV arms (2 mg vs. 5 vs. 10 mg, respectively) compared to 3% of TDF monotherapy. Biochemical response, defined as alanine aminotransferase (ALT) normalization, was observed in 43%, 50% and 40% in BLV arms vs. 6% in the TDF monotherapy arm. Combined response, defined as virological response plus ALT normalization, was achieved by 21%, 28% and 37% in BLV arms vs. 0% in patients receiving TDF monotherapy ($p < 0.05$ for all BLV arms vs. TDF). A dose-dependent decline of HDV-RNA and ALT levels was observed in all BLV arms, while HDV-RNA relapse occurred in 60%, 80% and 83% of viral responder patients 24 weeks after BLV discontinuation. HDV RNA relapse was associated with a moderate increase in ALT levels.[8]

Two treatment arms of the phase 2 **MYR203 study** included a total of 30 patients receiving BLV monotherapy (2 mg vs. 10 mg/day) in combination with TDF for 48 weeks. At Week 48, rates of HDV RNA undetectability were 13% vs. 47% in the 2 mg vs. 10 mg arm. The corresponding biochemical response rates were 73% and 40%, respectively, where the combined response rates resulted 13% for both arms. The primary study endpoint was HDV RNA undetectability at Week 72 (Week 24 off-therapy), which was achieved by 7% of the patients in the BLV 2 mg vs. 33% in the 10 mg arm.[9]

A longer 96 weeks course of BLV monotherapy was evaluated in the phase 2 **MYR204 study**, where 50 patients (45% with cirrhosis) received BLV at a dose of 10 mg/day. The interim analysis of the study reported a median 2.68 log IU/ml HDV RNA decline at Week 24. A virological response was achieved by 72% of patients (4% HDV RNA undetectable), while 64% of patients showed a biochemical response and 50% a combined response.[10]

The Phase 3, open-label, multicentre **MYR301 study** investigated efficacy and safety of BLV monotherapy in a large cohort of 150 HDV patients. As per study design. patients were randomized 1:1:1 to receive a 48 weeks delayed treatment with BLV 10 mg/day for 96 weeks (Arm A), BLV 2 mg/day for 144 weeks (Arm B) or BLV 10 mg/day for 144 weeks (Arm C). Interim study results were reported at Week 48: primary endpoint was combined response, while secondary endpoints included rates of HDV RNA undetectability, ALT normalization and changes in liver stiffness. Inclusion of patients with compensated (Child Pugh Score [CPT]-A6) cirrhosis was allowed and stratified across the three arms. At study start, mean age was 42 years, 57% males, 99% HDV genotype 1, 83% HBV genotype D, 10% HBeAg positive, 60% receiving NUC treatment, 56% previously treated with PegIFNα. Cirrhosis accounted for 47% in each study arm, mean liver stiffness was 14.7 kPa, ALT 111 U/L and HDV RNA 5 LogIU/ml. Among the 145 patients reaching Week 48 timepoint, 45% achieved the primary endpoint in Arm B (BLV 2 mg/day) vs. 48% in Arm C (BLV 10 mg/day) vs. 2% in Arm A (delayed treatment) ($p < 0.0001$). Rates of response were similar across all patient subgroups, including cirrhosis, in all treatment arms. At Week 48, virological response was achieved by 71% of patients in Arm B vs. 76% in Arm C vs. 4% in Arm A ($p < 0.0001$), while rates of HDV RNA undetectability were 12% vs. 20% ($p = 0.41$) in Arm B vs. C, respectively. Similar HDV RNA decline was observed with BLV 2 mg or 10 mg/day (mean HDV RNA at Week 48: 2.5 vs. 1.9 LogIU/ml, respectively). At Week 48, ALT normalized in 51% vs. 56% patients in arm B vs. C, while a significant reduction in liver stiffness was observed in immediate vs. delayed treatment arms. A dose-dependent elevation in serum bile acids was observed in both BLV arms, while pruritus was reported in 14% of patients. Injection site reactions occurred in 23% of cases, mostly mild to moderate in severity with a higher frequency in BLV 10 mg dose. No serious adverse events (SAE) related to BLV occurred and no patient discontinued BLV treatment. Overall, study results did not support an efficacy advantage in BLV 10 mg vs. 2 mg dosage.[11]

Main results of clinical trials with BLV monotherapy are summarized in Figure 1.

2.2 | Real-life studies

The **French compassionate use program (ATU)** included 78 patients (groups A and B) treated with BLV 2 mg/day monotherapy: mean age 42 years, 70% males, 64% with cirrhosis, 49% European ethnicity, median HDV RNA 6.3 LogIU/ml, 14% Hepatitis B e Antigen (HBeAg) positive, 18% HIV coinfected, 83% receiving NUC treatment. Results at months 12 and 18 were provided: patients in group A were still on-therapy, while group B discontinued BLV at month 12. In group A, rates of virological response were 66% and 61% at month 12 and 18, respectively. Rates of HDV RNA undetectability were 32% and 33%, respectively, while a combined response was achieved by 42% (month 12) and 36% (month 18). In group B, 62% of patients achieved a virological response at month 12 (HDV RNA undetectable in 46%); however, only 27% maintained this endpoint at month 18 (6 month after BLV discontinuation), rates of HDV

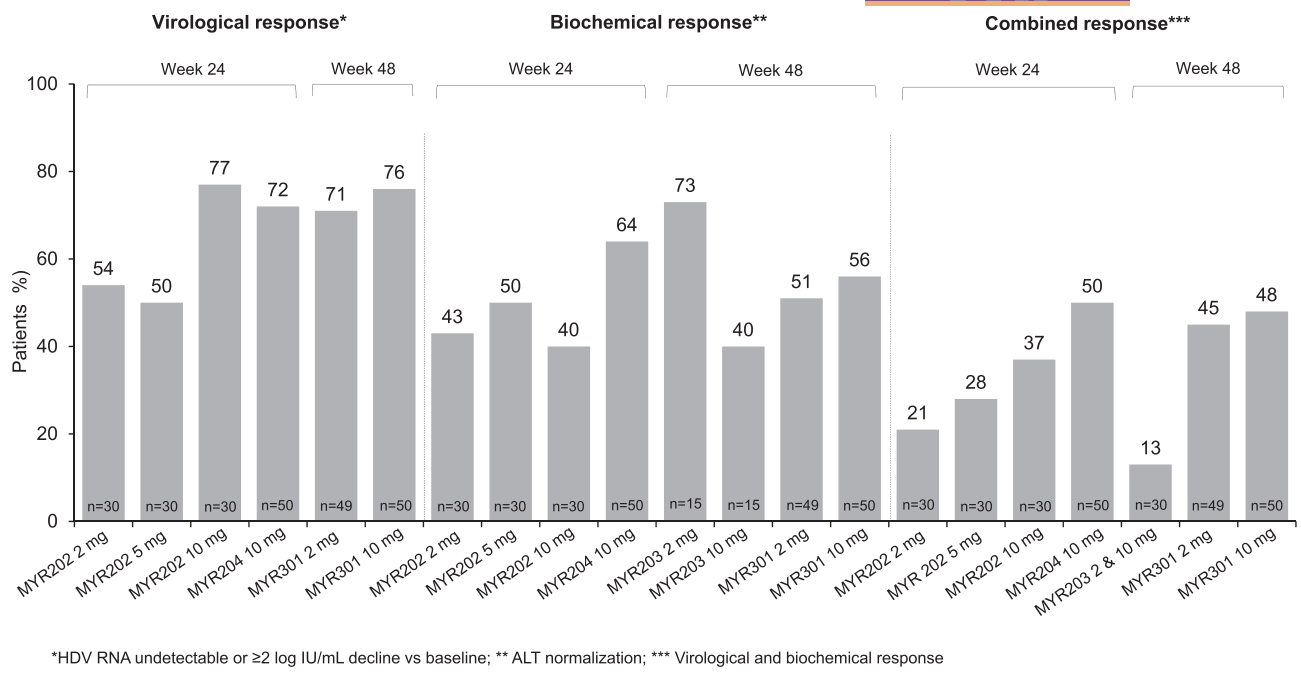


FIGURE 1 Virological, biochemical and combined response rates of BLV monotherapy in clinical trials.

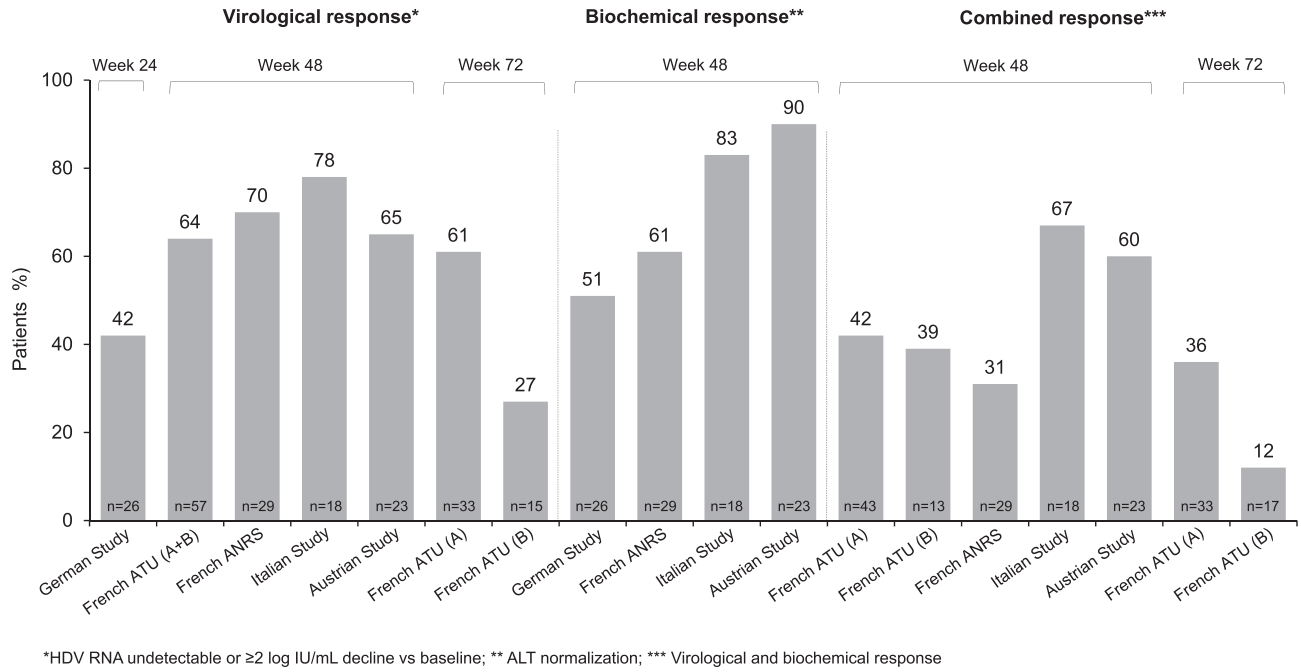


FIGURE 2 Virological, biochemical and combined response rates of BLV monotherapy in real-life studies.

RNA undetectability dropping to 20%. The corresponding figures for combined response were 39% and 12% at month 12 and 18, respectively.[12]

In the **French** multicentre **ANRS HDV cohort**, 65 patients received BLV 2 mg/day monotherapy: mean age 43 years, 72% males, 30% of European descent (35% from Sub-Saharian Africa), 59% with cirrhosis, 16% HIV-coinfected, 83% NUC-treated. Median HDV RNA at BLV start was 6.3 LogIU/ml, ALT 108 U/L. Median treatment duration was 17 months. After 24 weeks of BLV monotherapy, 39% of patients achieved a virological response (8% HDV RNA undetectable), ALT normalized in 54%, while a combined response was obtained in 17%. At Week 48 (data available for 29 patients), the corresponding figures were 70% virological response (HDV RNA undetectable in 17%), 61% ALT normalization, and 31% combined response, respectively.[13]

The **real-life study from Austria** included 23 patients starting BLV monotherapy (2 mg/day in $n = 22$, 10 mg/day, $n = 1$): mean age was 48 years, 43% males, 70% with cirrhosis, 84% under NUC

treatment, median ALT 71 U/L, HDV RNA 2.1×10^5 copies/ml. Patients received a response-guided therapy which included a 24–48 BLV monotherapy course followed by PegIFNα combination in cases of insufficient HDV RNA decline. At BLV monotherapy Week 48, a virological response was achieved by 65% of patients, ALT normalization occurred in 90% and a combined response was observed in 60%. Overall PegIFNα was subsequently added in 8 patients ($n = 2$ responders and 6 non-responders).[14]

In a multicentre **real-life study from Germany**, 109 patients received BLV 2 mg/day for 24 weeks: 43 (39%) with cirrhosis (decompensated in $n = 4$), median HDV RNA 5.7 LogIU/ml, ALT 116 U/L, 94% under effective NUC therapy. Complete data at Week 24 were reported for 26 patients: median HDV RNA declined by 2.2 LogIU/ml, 11 (42%) achieved the virological response, ALT normalized in 51% of patients, whereas 4 (15%) cases of primary virological non-response occurred. No significant changes in hepatic function parameters were observed (albumin, bilirubin, INR), platelet count increased, while Fibrosis score (FIB)-4 showed a significant improvement during BLV treatment. No serious adverse events were reported; fatigue ($n = 7$), pruritus ($n = 3$) and injection site reaction ($n = 1$) were the most common side effects. De novo decompensation occurred in two cases.[15] Germany also reported long-term outcomes at Weeks 52, 56 and 68 in three patients receiving BLV 2 mg/day monotherapy. All patients achieved a virological response at Week 24, that was maintained throughout Week 68 in two cases, while the other experienced HDV RNA breakthrough at Week 40.[16]

The **Italian real-life study** investigated safety and efficacy of BLV monotherapy 2 mg/day in 18 patients with compensated cirrhosis (CPT-A) and clinically significant portal hypertension (CSPH). Median age at BLV start was 48 years, 67% males, all Caucasian with HDV genotype 1, 67% previously treated with PegIFNα, all under effective NUC treatment for HBV. 14 (78%) patients had oesophageal varices, median spleen size was 17 cm, ALT 106 U/L, HDV RNA 4.9 LogIU/ml. Following 48 weeks of BLV monotherapy, HDV RNA declined by 3.1 (0.2–4.3) log IU/ml ($p < 0.001$ vs. baseline), becoming undetectable in 5 patients (23%). A virological response was observed in 14 (78%) patients while a non-response in 2 (11%). ALT decreased to 35 (15–86) U/L ($p < 0.001$ vs. baseline), normalizing in 83% of patients (biochemical response). A combined response was observed in 67% of the patients. Significant improvement of most biochemical variables (AST, GGT, IgG, gammaglobulins) was reported. Concerning liver function parameters, albumin values significantly increased and bilirubin remained stable. Liver stiffness measurement significantly improved in the subset of viral responder patients, while platelet count was unchanged. None of the patient developed decompensating events or HCC. BLV treatment was very well tolerated, no patient discontinued treatment and no adverse events were reported, including injection site reactions. The increase of bile acids was fully asymptomatic.[17]

Main results of real-life studies with BLV monotherapy are summarized in Figure 2.

Data are scarce regarding **long-term BLV monotherapy**, as only few case reports have been published. Two patients with compensated HDV-related cirrhosis (Italy $n = 1$, Austria $n = 1$) received BLV monotherapy for 3 years. ALT normalization was achieved by Week 28 in both cases and HDV RNA became undetectable before Week 52. Biochemical and virological response were maintained throughout 3 years of BLV monotherapy; in the Italian patient, BLV dose was reduced from 10 mg to 2 mg/day with persistence of HDV RNA undetectability.[18] In this former patient, prolonged BLV treatment resulted in improved clinical outcomes: indeed, liver stiffness, platelets count and albumin levels significantly improved, alpha-fetoprotein (AFP) levels normalized and pre-treatment small oesophageal varices regressed. Moreover, histological and laboratory features of autoimmune hepatitis related to HDV infection resolved. After 3 years of BLV monotherapy, treatment was discontinued and HDV RNA persisted undetectable at post-treatment Week 48; a liver biopsy performed at this timepoint showed minimal features of inflammation and a significant improvement of liver fibrosis (Ishak score Grading 1 Staging 4). HBsAg stained positive in 0.4% of the biopsy while HBcAg and HDAg stained negative; intrahepatic HDV RNA and cccDNA tested negative.[19]

3 | BLV IN COMBINATION WITH PEG-IFNA

3.1 | Clinical trials

In the phase 2 **MYR203** study, 60 patients were randomized to receive either PegIFNα monotherapy or in combination with BLV 2 at different doses (2 mg vs. 5 mg vs. 10 mg/day) for 48 weeks. At the end of treatment, HDV RNA resulted undetectable in 80%, 87% and 80% of patients in BLV arms (2 mg, 5 mg, 10 mg, respectively) vs. 13% of PegIFNα monotherapy. The corresponding figures for biochemical response were 27%, 47%, 27% vs. 27%, while a combined response was achieved by 20%, 33%, 20% vs. 7%. HDV RNA undetectability at Week 72 (24 weeks off-treatment), that was the primary endpoint of the study, was achieved by 53%, 26% and 7% of patients in BLV arms, respectively, compared to 0% of the PegIFNα monotherapy arm. HBsAg >1 Log decline at Week 72 was achieved in 40% of patient receiving PegIFNα + BLV 2 mg vs. 13% for BLV 5 mg and 10 mg vs. 4% for PegIFNα monotherapy. 27% of patients treated with PegIFNα + BLV 2 mg and 7% of patients treated with PegIFNα + BLV 10 mg experienced HBsAg loss. Off-therapy HDV RNA responses at Week 72 were observed in patients achieving HBsAg decline.[9]

Overall, 124 CHD patients (35% with cirrhosis) in three arms of the phase 2 **MYR204 study** received PegIFNα-based strategies in combination with BLV. As per study design, patients were randomized to receive: PegIFNα monotherapy for 48 weeks ($n = 24$ patients); PegIFNα + BLV 2 mg/day for 48 weeks, followed by 48 weeks of BLV 2 mg monotherapy ($n = 50$ patients); PegIFNα + BLV 10 mg/day for 48 weeks, followed by 48 weeks of BLV 10 mg monotherapy ($n = 50$ patients). Following 24 weeks of treatment, median HDV RNA decline in the PegIFNα monotherapy arm was 2.01 LogIU/ml, while combination with BLV strategy resulted in a more pronounced

decline in HDV RNA (3.78 LogIU/ml in BLV 2 mg vs. 4.11 LogIU/ml in BLV 10 mg). Virological response at Week 24 was achieved in 38% vs. 88% and 92% in the PegIFNα monotherapy vs. combination with BLV 2 mg and 10 mg, respectively. Rates of HDV RNA undetectability were 13% vs. 24% vs. 34%, respectively. Only 13% of patients treated with PegIFNα monotherapy showed a biochemical response, in contrast to 30% and 24% of patients in the combination BLV groups. Rates of combined response were 30% and 24% in the PegIFNα + BLV 2 mg and PegIFNα +10 mg, respectively.[10]

Main results of clinical trials with PegIFNα + BLV combination are summarized in Figure 3.

3.2 | Real-life studies

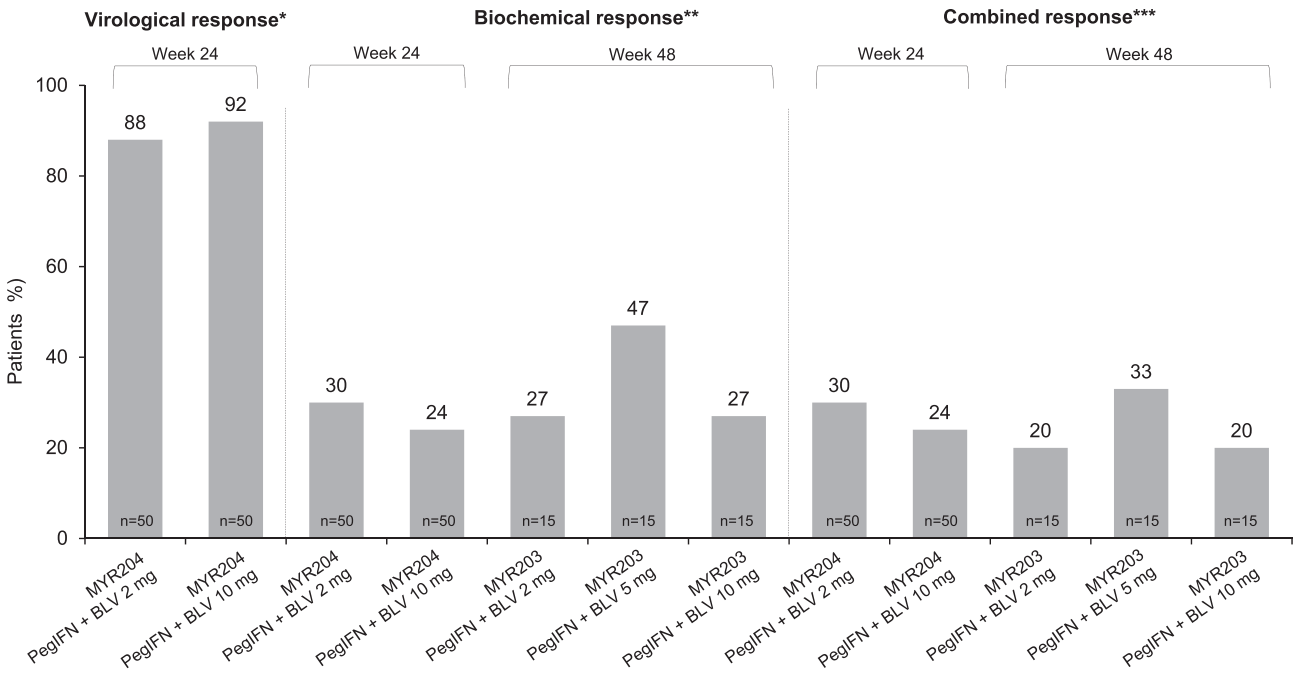
Overall, 68 patients (Groups C-D-E) received BLV in combination with PegIFNα in the **French compassionate Use Program (ATU)**: mean age was 41 years, 63% males, 65% with cirrhosis, 36% European, 5% HBeAg positive, 8% HIV-coinfected and 71% NUC-treated. Median HDV RNA was 6.3 LogIU/ml, ALT 126 U/L. In group C (BLV + PegIFNα ongoing), rates of virological response were 74% and 71% at month 12 and 18, respectively (HDV RNA undetectable in 61% and 57%). Rates of combined response were 22% at month 12, rising to 41% at month 18. Patients in group D received BLV + PegIFNα for 12 months followed by BLV monotherapy: a virological response was achieved by 95% of patients at month 12 (HDV RNA undetectable in 77%) and was maintained in 74% of patients (HDV RNA undetectable 61%) at month 18 (BLV monotherapy ongoing, 6 months after PegIFNα discontinuation). Rates of combined response were 50% and 55% at months 12 and 18, respectively. Patients from group E received BLV + PegIFNα combination for 12 months: 63% achieved a virological response (56% HDV RNA undetectable) and 19% a combined response at month 12 (EOT). At month 18 (6 months off-therapy), still 67% of patients maintained a virological response (50% HDV RNA undetectable) and a combined response was observed in 42%.[12]

Among the 115 patients treated in the **French ANRS HDV cohort**, 50 received BLV + PegIFNα combination for a median duration of 18 months: mean age 41 years, 68% males, 52% of Sub-Saharian ethnicity, 9% HIV-coinfected, 52% with cirrhosis, 78% under NUC treatment, median HDV RNA 6.4 LogIU/ml, ALT 128 U/L. After 24 weeks of BLV + PegIFNα treatment, a virological response was achieved by 84% of patients, HDV RNA was undetectable in 44%, ALT normalized in 35% and a combined response was reported in 34%. In the 26 patients with available Week 48 data, the corresponding figures were 85% virological response (62% HDV RNA undetectable), 39% ALT normalization, 35% combined response. At multivariate analysis, receiving PegIFNα for 12 weeks was associated with viral response (OR 8.4; 95% CI 3.4–20.8, $p < 0.0001$). Overall, 6 patients discontinued IFN treatment, while, as expected, rates of side effects were significantly higher with BLV + PegIFNα combination than BLV monotherapy.[13]

Main results of real-life studies with PegIFNα + BLV combination are summarized in Figure 4.

4 | SAFETY

In clinical trials and real-life reports, BLV monotherapy was well tolerated: no serious adverse events (SAEs) related to study drug



*HDV RNA undetectable or ≥2 log IU/mL decline vs baseline; ** ALT normalization; *** Virological and biochemical response

FIGURE 3 Virological, biochemical and combined response rates of BLV + PegIFNα combination in clinical trials.

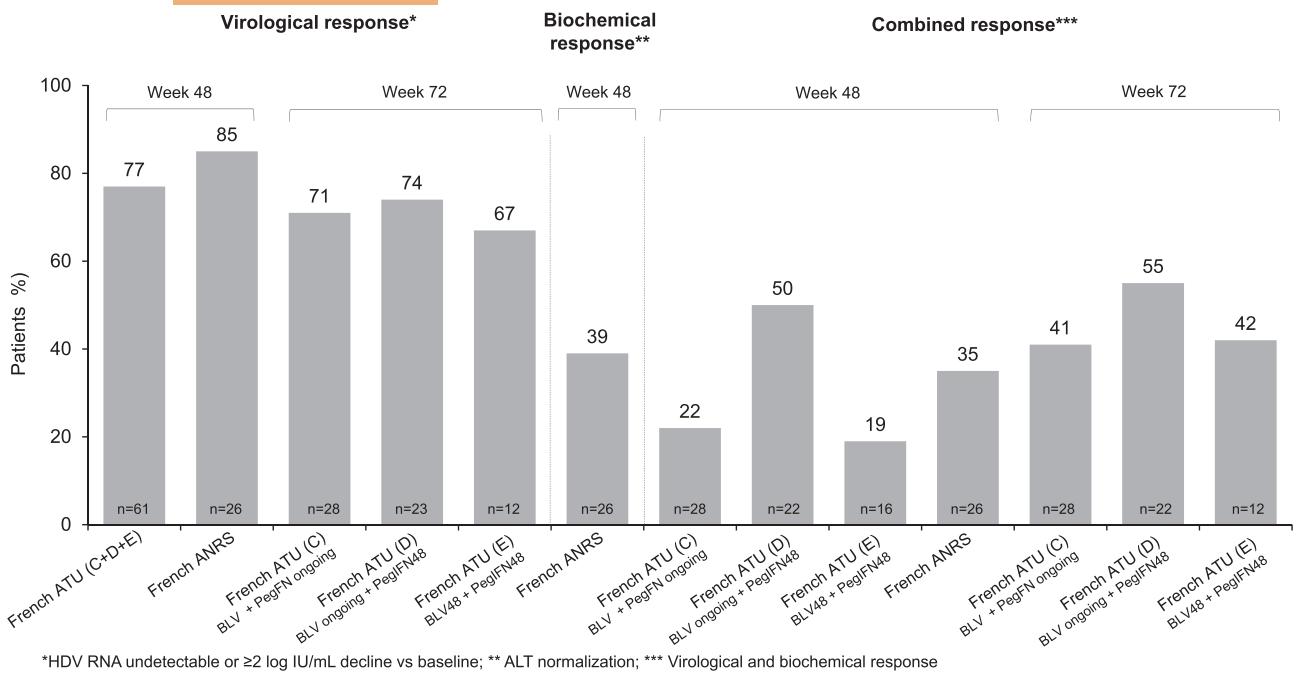


FIGURE 4 Virological, biochemical and combined response rates of BLV + PegIFNα combination in real-life studies.

were observed reported in clinical trials, as well as side effects leading to treatment discontinuation. Also in real-life studies, rates of BLV discontinuation due to side were negligible, except for some experiences (French ATU). In the MYR301 study, mild and dose-dependent injection-site reactions were reported: 6% in the BLV 2 mg/day arm vs. 26% in the BLV 10 mg/day group. In real-life experiences, injection site reactions were rarely observed with the 2 mg/day dose. As expected by BLV mechanism of action, increase of bile acids due to NTCP receptor blockage was reported in both clinical and real-life studies: in the vast majority of cases, the bile acid increase was fully asymptomatic. Recently, a case of immediate-type hypersensitivity reaction to BLV was described in an Austrian compensated cirrhotic patient: progressive pruritus, swelling of the upper extremities, face, lips and dyspnoea were indicative of type-1 allergic reaction. These symptoms immediately resolved after treatment discontinuation; however, as the patient had a strong clinical need for BLV administration, a desensitization strategy was applied and led to continue BLV treatment without any further complications.[20]

The addition of PegIFNα to BLV was associated with expected PegIFNα-related side effects, resulting in increased rates of treatment discontinuation in patients receiving BLV combination with PegIFNα compared to BLV monotherapy alone.

5 | SUMMARY AND CONCLUSIONS

For the first time since HDV discovery, a new anti-HDV treatment option is available with conditional approval of a regulatory agency (EMA). In clinical trials, BLV has demonstrated significant rates of virological and biochemical response, coupled with good safety profile. These encouraging data have been confirmed by real-life reports also in patients with advanced compensated cirrhosis. Prolonged HDV RNA suppression may result in improved clinical outcomes, that is liver function tests and some cirrhosis-associated complications. Combination with PegIFNα has shown to provide additional and synergistic effects in term of viral response.

However, many issues have still to be solved: first of all, optimal treatment duration is currently unknown. While a finite treatment duration could be envisaged with addition of PegIFNα to enhance response rates, many HDV patients are not PegIFNα candidates due to advanced liver disease and could require a prolonged BLV monotherapy treatment approach. More studies are needed to characterize mechanisms of viral control, define predictors of response and criteria for BLV discontinuation. This is of crucial importance in patients with advanced cirrhosis, where flares associated with viral relapse after BLV discontinuation could result in liver decompensation. While EMA approval suggests that treatment should be continued as long as a clinical benefit is demonstrated, more data are needed in order to assess long-term outcomes with BLV treatment and define robust treatment endpoints associated with significant benefits in term of liver-related mortality and survival.

AUTHOR CONTRIBUTIONS

Concept and design, interpretation of the data, drafting the article and critical revision: ED, MPA, PL.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

Elisabetta Degasperi: Advisory Board: AbbVie; Speaking and teaching: Gilead, MSD, AbbVie. Maria Paola Anolli: nothing to disclose. Pietro Lampertico: advisor and speaker bureau for BMS, Roche, Gilead Sciences, GSK, MSD, Abbvie, Janssen, Arrowhead, Alnylam, Eiger, MYR Pharma, Antios, Aligos, Vir.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

All authors approved the final version of the manuscript.

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