Case Report

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A 3-year course of bulevirtide monotherapy may cure HDV infection in patients with cirrhosis

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Summary

Bulevirtide recently received conditional approval from the EMA for the treatment of chronic hepatitis delta, but the ideal duration of therapy is unknown. Herein, we describe the first case of hepatitis delta cure following 3 years of bulevirtide monotherapy in a patient with compensated cirrhosis and esophageal varices. During the 72-week off-bulevirtide follow-up, virological and biochemical responses were maintained. In the off-therapy liver biopsy, intrahepatic HDV RNA and hepatitis D antigen were undetectable, <1% of hepatocytes were hepatitis B surface antigen positive and all were negative for hepatitis B core antigen. Ishak grading and staging were improved following treatment.

Introduction

Chronic hepatitis delta (CHD) is a severe form of chronic viral hepatitis, affecting approximately 12-72 million individuals worldwide. For many years, the only therapeutic option has been the off-label administration of pegylated-interferon-alpha (PegIFNα), an approach characterized by suboptimal efficacy, unfavorable safety profile and several contraindications.[1] In 2020, the EMA conditionally approved bulevirtide (BLV), the first-in-class entry inhibitor of HDV/HBV, for the treatment of adult patients with compensated CHD.[2] The promising results from phase II and III studies[3,4] were confirmed by preliminary real-life studies.[5–7] We have previously reported the real-life safety and effectiveness of BLV monotherapy administered for 144 weeks in patients with compensated cirrhosis.8 We hereby describe one of these patients, a 54-year-old Caucasian male who showed a sustained off-BLV cure of HDV infection, maintaining HDV RNA undetectability both in serum and liver tissue.

Materials and methods

Clinical variables were assessed according to international guidelines. HDV RNA was quantified by RoboGene® (HDV RNA quantification 2.0; Aj-Roboscreen, Jena, Germany; lower limit of detection [LOD] 6 IU/ml). HBV DNA was quantified by Abbott Real*Time* HBV (Abbott Diagnostics, Rome, Italy; lower limit of quantification [LLOQ] 10 IU/ml). Serum hepatitis B surface antigen (HBsAg) was quantified by Elecsys HBsAg II quantitative assay on the Cobas® e801 Analyzer (Roche Diagnostics Gmbh. Mannheim. Germany: LLOQ 0.05 IU/ml). Serum HBV core-related antigen (HBcrAg) was assessed with LUMIPULSE® G HBcrAg assay (Fijirebio Europe, LOD 2 $\log_{10}$ U/ml). Serum HBV RNA was quantified by an in-house real-time PCR technique (Leipzig, LOD 160 cp/ml) in the first year of therapy, and then by a real-time PCR-based investigation assay (Roche Diagnostics, Pleasanton, Ca, USA, LLOQ 10 cp/ml).

On liver tissue, hepatitis D antigen (HDAg), HBsAg and hepatitis B core antigen (HBcAg) were determined in formalin-fixed and paraffin embedded liver tissue sections by immunohistochemistry using the Dako EnVision®+ System-HRP (Dako, Agilent Technologies). A primary antibody detecting HDAg (kindly provided by Prof. John Taylor) was used in a 1:10,000 dilution. For HBsAg, target retrieval was performed in Tris-EDTA/0.05% Tween (pH 9) and an HBsAg-specific antibody (Biolegend #932302) was used in a 1:5,000 dilution. For HBcAg, target retrieval was performed in Tris-EDTA (pH 9) and a primary antibody detecting HBcAg (abcam #8639) was used in a 1:10,000 dilution. Stained sections were analyzed by brightfield microscopy (BZ-X710, Keyence, Osaka, Japan). Total RNA was extracted from frozen liver biopsy material with the RNeasy Mini Kit Qiagen, Hilden, Germany) and intrahepatic HDV RNA levels were quantified by quantitative reverse-transcription PCR. HDV-specific T-cell responses were analyzed using overlapping peptides (OLPs) spanning the total large HDAg (15-mers, sliding by four amino acid residues). Peripheral blood mononuclear cells were cultured in the presence of all 51 OLPs for 10 days, followed by intracellular interferon-gamma staining with pools of four OLPs. Positive OLP pools were further resolved to individual positive OLPs.

Keywords: Bulevirtide; HDV; HDV RNA; HBV; compensated cirrhosis; sustained virological response; clinically significant portal hypertension; liver fibrosis; HBcrAg; PBMC.
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Clinical case

The biochemical and virological outcomes of a 3-year treatment course of BLV monotherapy have already been described: the patient is referred to as "Patient 2" in the paper.[8] Briefly, the patient was known to have compensated cirrhosis (Child-Pugh Score A5) complicated by clinically significant portal hypertension, *i.e* splenomegaly and small esophageal varices (F1, red color sign negative), since 2010. He was infected with HBV genotype D and HDV genotype 1. He was on dietary therapy for type 2 diabetes mellitus but had a BMI within the normal range (22.7 kg/m^2). A liver biopsy performed in 2010 (liver biopsy #1) showed cirrhosis with moderate to severe HDV-related hepatitis (Ishak score: grade [necroinflammatory activity] 9, stage [fibrosis] 6) and a significant plasmacellular component. He had been on tenofovir disoproxil fumarate since June 2012 to control HBV replication. In 2018, due to the severity of liver disease, thrombocytopenia, and presence of autoimmune stigmata, thereby contraindicating PegIFNα therapy, BLV treatment was requested for "compassionate use".

The patient received BLV monotherapy for 3 years, 10 mg/day for 76 weeks and 5 mg/day for an additional 68 weeks. HDV RNA declined rapidly and became undetectable at week 28, while alanine aminotransferase normalized at week 8, shortly followed by aspartate aminotransferase, alkaline phosphatase, albumin, pseudo-cholinesterase and alpha-fetoprotein. A liver biopsy performed on therapy at week 72 showed a reduction of necroinflammation and plasma cells, and improvement of features of autoimmune hepatitis but without significant changes in liver fibrosis (Ishak score: grade 7, stage 6). At week 96 on therapy, an esophagogastroduodenoscopy showed full regression of esophageal varices.

After 3 years of continuous treatment, BLV was discontinued in 2021. Table 1 shows the time course of virological, biochemical and clinical variables during and after BLV withdrawal. In the 72 weeks of post-treatment follow-up, HDV RNA remained persistently undetectable (target not detected), transaminases and alkaline phosphatase remained within the normal range as did alpha-fetoprotein levels, together with all other markers of liver function. Gamma glutamyltransferase did not normalize throughout the study period, likely because of the presence of type 2 diabetes. Gamma-globulins and immunoglobulin G, which had already normalized during BLV therapy, persisted in the normal range. Autoantibodies were retested during follow-up and were persistently undetectable up to 48 weeks after treatment cessation. Platelet counts normalized

Table 1. Time course of biochemical and virological variables during and after BLV treatment.

Variables	Baseline (pre-treatment)	End of therapy with BLV (week 144)	Off-therapy week 12	Off-therapy week 24	Off-therapy week 36	Off-therapy week 48	Off-therapy week 72
ALT (IU/L)/AST (IU/L)	232/179	28/36	23/30	44/50	31/36	30/33	20/26
ALP (IU/L)/GGT (IU/L)	185/231	85/110	82/77	88/226	110/72	56/68	65/89
Total bilirubin (mg/dl)	0.4	0.6	0.6	0.6	0.6	0.7	0.6
pCHE (IU/L)	4,479	7,805	7,200	8,440	8,313	8,923	7,816
Albumin (g/dl) /gamma-globulin (g/dl)	3.6/2.9	4.6/1.0	4.5/1.0	4.5/1.1	4.3/1.0	4.6/1.1	4.5/1.0
Immunoglobulin G (mg/dl)	3,077	1,285	1,240	1,160	1,185	1,221	1,129
AFP (ng/dl)	21	4	3	4	4	5	3
PT-INR	1.1	1.1	1.1	1.0	1.2	1.1	1.2
Platelet count (x10^9/L)	74	110	137	115	144	144	160
ANA/AMA/ASMA/LKM	-/-/-/-	-/-/-/-	-/-/-/-	-/-/-/-	—	-/-/-/-	—
Liver stiffness (kPa)	17.6	10.9	8.5	11.5°	—	10.6	6.9
Spleen length (cm)	14.0	13.0	—	14.5	—	14.5	12.2
Creatinine (mg/dl)	0.82	0.84	0.93	0.99	0.84	0.93	0.8
HBsAg (IU/ml)	9,091	5,045	2,873	3,238	2,347	2,316	2,014
HBcrAg (log U/ml)	4.5	3.5	3.5	3.4	3.4	3.4	—
HBV DNA (IU/ml)	TND	TND	TND	TND	TND	TND	TND
HBV RNA (cp/ml)	<160*	<10§	<10	<10	—	<10	—
HDV RNA (IU/ml)	392,000	TND	TND	TND	TND	TND	TND
Bile acids (μmol/L)	35	55	8	15	—	11	1
Esophageal varices on EGD	F1 RCS-†	No×	—	—	—	No	—
Intrahepatic HBsAg	—	Focally positive (1.4% of liver biopsy)■	—	—	—	Focally positive (0.4% of liver biopsy)	—
Intrahepatic HBcAg	—	Negative■	—	—	—	Negative	—
Intrahepatic HDAg	—	Negative■	—	—	—	Negative	—
Intrahepatic HDV RNA	—	Negative■	—	—	—	Negative	—

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; BLV, bulevirtide; EGD, esophagogastroduodenoscopy; GGT, gamma glutamyltransferase; HBcAg, hepatitis B core antigen; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; HDAg, hepatitis D antigen; LKM, liver kidney microsomal antibodies; LLOQ, lower limit of quantification; pCHE, pseudo-cholinesterase; PT-INR, prothrombin time-international normalized ratio; RCS, red color sign; TND, target not detected.

°Lack of adequate fasting time.

*Performed with in-house real-time PCR technique (Leipzig, LOD 160 cp/ml).

§Performed using a real-time PCR-based investigation assay (Roche Diagnostics, Pleasanton, CA, USA, LLOQ 10 cp/ml).

†F1: small varices.

×Regression of esophageal varices was already demonstrated at the EGD performed on therapy at week 80.

■Detected in the biopsy performed on therapy at week 72.

and liver stiffness measurement significantly declined (from 17.6 at baseline to 6.9 kPa at week 72 off-therapy). HBsAg and HBcrAg declined (4 log IU/ml *vs*. 3.3 log IU/ml and 4.5 log U/ml *vs.* 3.4 log U/ml, respectively). Serum HBV DNA as well as HBV RNA remained undetectable at all time-points, but treatment with tenofovir disoproxil fumarate was maintained. Bile acids normalized upon BLV discontinuation. A new esophagogastroduodenoscopy confirmed the absence of esophageal varices, while an abdominal MRI showed a stable spleen size and no focal liver lesions.

A third liver biopsy that was performed at week 48 post treatment showed minimal features of inflammation together with a significant improvement of liver fibrosis (Ishak score: grade 1, stage 4). Hallmarks of chronic hepatitis were no longer detectable, and features of autoimmunity had completely resolved. A few clusters of hepatocytes with a cytoplasmatic distribution of HBsAg were present in the biopsy, while liver tissue was negative for core antigen (HBcAg). Of note, both HDAg by immunostaining and intrahepatic HDV RNA by qPCR were undetectable. Very low amounts of pregenomic RNA but higher amounts of subgenomic HBV RNAs were detected, suggesting that at least part of the HBsAg staining may derive from integrated HBV DNA. Given these compelling results, intrahepatic virological analyses were retrospectively performed on the liver biopsy taken at week 72 on therapy: both HDAg and HDV RNA were undetectable, core antigen stained negative while a similar distribution of cytoplasmatic HBsAg was detected as in the off-therapy biopsy (Table 1 and Fig. 1A).

HDV-specific T-cell responses were analyzed at three time-points off-therapy (week 6, 20, and 48), using a very sensitive peptide-specific expansion protocol. Of note, only subtle and fluctuating HDV-specific CD4+ and CD8+ T-cell responses were detectable. Specifically, a CD4+ T-cell response targeting $HDAg_{49-63}$ was detectable at week 6 off-therapy, but not at the two later time-points (Fig. 1, panel B1). Similarly, a CD8+ T-cell response targeting $HDAg_{189-199}$ was detectable at week 6 and 48 off-therapy, but not at the time-point in between (Fig. 1, panel B2). Both responses were minor when compared to responses identified in a control cohort of 14 BLV-naïve patients with CHD and cirrhosis (ring graphs and right columns in Fig. 1, panel B1–B2). Indeed, in the control cohort, 5/6 CD4+ responses identified in three of the patients and 11/17 CD8+ responses detected in six of the patients were more vigorous than the off-treatment responses in the cured case. These findings suggest that the presence or emergence of these cells is not a major contributor to HDV cure.

Discussion

The recent approval by the EMA of BLV treatment for adult patients with compensated CHD has revolutionized the antiviral management of this difficult-to-treat disease, for which no FDA- nor EMA-approved therapies were previously available. Among several open issues, the ideal duration of BLV monotherapy is yet to be defined as the EMA states that BLV treatment should be continued for as long as a clinical benefit can be demonstrated. The phase III MYR301 registration study whose aim is to define if a 3-year course of BLV monotherapy may lead to HDV cure, is still ongoing.

Our case report demonstrates for the first time that HDV infection may be cured after a 3-year course of treatment with BLV monotherapy, even in a difficult-to-treat patient with compensated cirrhosis and esophageal varices. Virological, biochemical as well as intrahepatic analyses are consistent with this hypothesis: 48-72 weeks after BLV discontinuation there was no evidence of liver or serum HDV replication despite the

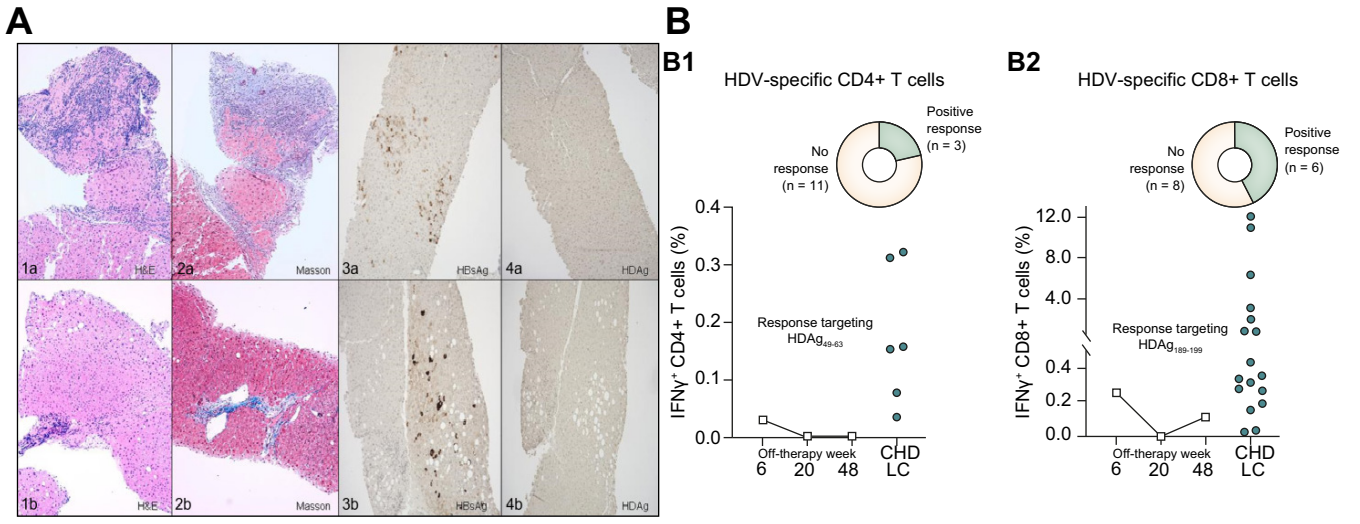

Fig. 1. Histological changes during and after therapy and immunological changes after therapy. (A) Comparison of the liver biopsies performed during BLV treatment, at week 72 (1a-4a) and 48 weeks after BLV discontinuation (1b-4b). On-therapy liver biopsy: 1a, hematoxylin and eosin; 2a, Masson's trichrome stain; 3a, HBsAg staining; 4a, HDAg staining. Off-therapy liver biopsy: 1b, hematoxylin and eosin; 2b, Masson's trichrome stain; 3b, HBsAg staining; 4b, HDAg staining. (B) HDV-specific T-cell response at off-therapy time-points week 6, 20, and 48. Peripheral blood mononuclear cells from off-therapy week 6, 20, and 48, respectively, were analyzed for HDV-specific T-cell responses in a sensitive peptide-specific culture approach using OLPs covering the complete HDAg. OLP $HDAg_{49-63}$ tested positive for a CD4+ response at the first time-point (B1). OLPs $HDAg_{185-199}$ and $HDAg_{189-203}$ tested positive for a CD8+ response at two time-points, indicating that the overlapping region $HDAg_{189-199}$ contained the viral target (B2). The strength of these responses was compared to responses in 14 BLV-naïve patients with CHD and cirrhosis tested by the same approach. The proportions of patients with a positive response are indicated in the ring charts; positive responses in these patients are displayed in the column graph by strength (B1 and B2, right columns). BLV, bulevirtide; CHD, chronic hepatitis delta; HBsAg, hepatitis B surface antigen; HDAg, hepatitis D antigen; OLP(s), overlapping peptide(s). (This figure appears in color on the web.)

persistence of HBsAg. Liver specimens tested negative for HDAg staining and for covalently closed circular DNA, even though serum HBsAg and HBcrAg remained positive, though at lower levels than pre-treatment. This could be due to the sensitivity and relative specificity of the covalently closed circular DNA assay and/or to sampling variations in liver tissue. These intrahepatic findings were also confirmed in the second liver biopsy that was performed at week 72 on treatment, *i.e.* 72 weeks before BLV withdrawal. Of note, histological features of HDV-related autoimmune hepatitis disappeared and necroinflammatory activity and fibrosis significantly improved in the off-treatment liver biopsy.

It has previously been reported that HDV infection may be associated with autoimmune features, including autoimmune hepatitis,[9] but, to our knowledge, this is the first time these features have been shown to resolve upon BLV-induced HDV cure.

Clinically, all the BLV treatment-induced clinical and biochemical benefits were confirmed during the off-treatment follow-up: normal liver enzymes, preserved synthetic function, normalization of immunoglobulin G and gamma-globulins, regression of esophageal varices, reduction in liver stiffness measurement by FibroScan, and normalization of platelet count. The presence of a faint HDV-specific T-cell response after HDV clearance could indicate that HDV-specific T cells are not mandatory for sustained clearance of chronic HDV infection. Nevertheless, the faint T-cell response could also be linked to the patient's age and the homing of HDV-specific T cells preferentially into the liver.[10]

We acknowledge that our observations have some limitations. Firstly, being a case report makes it impossible to draw generalized conclusions. Another potential limitation of our observations is that BLV has been approved by the EMA at the 2 mg/day dosage,[2] while our patient has received higher doses. However, in the phase III registration study, virological and biochemical responses at week 48 in patients treated with BLV 2 mg/day were similar to those observed in patients treated with 10 mg/day.[4] Thirdly, although our patient was monitored off-therapy for 72 weeks, we cannot exclude that a late relapse may still occur as described previously following PegIFNα treatment.[11]

In conclusion, this case report demonstrates that HDV can be cured by a finite 3-year course of BLV monotherapy even in difficult-to-treat patients, such as those with compensated cirrhosis and esophageal varices.

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Abbreviations

BLV, bulevirtide; CHD, chronic hepatitis delta; HBsAg, hepatitis B surface antigen; HBcrAg, HBV core-related antigen; HDAg, hepatitis D antigen; HBcAg, hepatitis B core antigen; LOD, lower limit of detection; LLOQ, lower limit of quantification; OLPs, overlapping peptides; PegIFNα, pegylated-interferon-alpha.

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Conflict of interest

Elisabetta Degasperi: Advisory Board: AbbVie; Speaking and teaching: Gilead, MSD, AbbVie; Angelo Sangiovanni: Speaker: Abbvie, MSD, Gilead; Christoph Neumann-Haefelin: Speaker Bureau: Abbvie, Gilead, GSK, MSD. Maura Dandri: Advisor: Gilead and Aligos. Research collaboration with Gilead, MYR Pharma/Hepatera Ltd. and HUMABS BioMed; Fabien Zoulim: Advisor for Aligos, Antios, Arbutus, Assembly, Gilead, GSK, MYR Pharma, Roche; Pietro Lampertico: Advisor and speaker bureau for BMS, Roche, Gilead, GSK, MSD, AbbVie, Janssen, Arrowhead, Alnylam, Eiger, MYR Pharma, Antios, Aligos. Other authors have nothing to disclose.

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

Authors' contributions

Concept and design**:** Maria Paola Anolli, Elisabetta Degasperi, Pietro Lampertico. Data collection: Maria Paola Anolli, Elisabetta Degasperi, Angelo Sangiovanni. Writing of the article**:** Maria Paola Anolli, Elisabetta Degasperi, Pietro Lampertico. Virological analysis: Caroline Scholtes, Fabien Zoulim. Intrahepatic analysis: Lena Allweiss, Marco Maggioni. Immunological analysis: Valerie Oberhardt, Christoph Neumann-Haefelin. Critical revision of the manuscript: Christoph Neumann-Haefelin, Maura Dandri, Fabien Zoulim, Pietro Lampertico. All authors approved the final version of the manuscript.

Data availability statement

Data from the present study is kept confidential but can be provided upon direct request to the authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.12.023.

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Author names in bold designate shared co-first authorship

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