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Abstract

Background and Aims: Hepatitis B/D coinfection poses a high risk for the progression to severe liver disease. In July 2020, bulevirtide (2mg/day) was approved in the European Union for the treatment of chronic hepatitis delta. The drug blocks the bile salt transporter NTCP, which is also the entry receptor for Hepatitis B and D viruses. Here we describe the first sixteen weeks of therapy with bulevirtide in hepatitis delta patients who were included in an early access programme in a tertiary care centre in Germany.

Method: We included patients with active hepatitis B/D coinfection who were eligible for the early access programme. The main exclusion criteria were liver cirrhosis Child-Pugh Score B or C, thrombocytopenia below 50/nl, hepatocellular carcinoma or planned pregnancy. All included patients (n=8) received detailed information and training for drug administration.

Results: All patients (n=8) were under concomitant therapy with nucleoside/nucleotide analogues. None had a concomitant interferon treatment, mostly due to patients' reticence or contraindications. One patient dropped out shortly after inclusion because of a newly diagnosed hepatocellular carcinoma, and seven patients completed at least 16 weeks of therapy. Mean ALT values before treatment (baseline) were 78 U/l and declined to 39 U/l after 16 weeks. Mean HDV-RNA was 10,902,457 cop/ml at baseline and dropped to 3,740,569 cop/ml. One patient showed no significant biochemical or viral response and was discontinued. We observed no relevant side effects apart from asymptomatic elevation of bile acids.

Conclusion: These are the first real life data on bulevirtide therapy in Germany. Overall, we observed a favorable safety profile as well as a marked biochemical and virological response in the majority of our patients. However, middle- and long-term data are needed to evaluate the impact of bulevirtide on clinical endpoints in hepatitis delta patients.

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First real-life experiences with bulevirtide for the treatment of hepatitis delta – data from a tertiary reference centre in Germany

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1 Background and Aims

Hepatitis B/D coinfection is associated with rapid progression to severe liver disease and hepatocellular carcinoma (1) and poses a relevant public health challenge in numerous countries (2-5). Effective drug therapy options for chronic hepatitis D (CHD) are still needed. Until 2020 interferon alpha was the only treatment option for HDV infection. With serious side effects and a limited efficacy of about thirty percent, it remains an ineffective option for a majority of patients (6-9).
In July 2020, bulevirtide (2mg/day) was approved in the European Union for the treatment of CHD. The drug blocks the bile salt transporter NTCP, which is also the entry receptor for Hepatitis B and D viruses (10, 11). In Germany it received market approval in September 2020. An **early access programme** allowed for a therapy start with bulevirtide (BLV) around six weeks before market approval. Here we describe the first sixteen weeks of therapy with bulevirtide in hepatitis delta patients who were included in an early access programme in the hepatology outpatient clinic of Charité University Medicine Berlin, Germany.

2 Method

We included patients with **active hepatitis B/D coinfection** who were eligible for the early access programme. The main exclusion criteria were liver cirrhosis Child-Pugh Score B or C, thrombocytopenia below 50/nL, hepatocellular carcinoma or planned pregnancy. Patients were monitored in a monthly interval in our outpatient clinic.
All included patients received detailed information and training for drug administration.
We used a mixed effects model to control for interindividual variation and applied log transformation to address skewed data.

3 Results

Patient characteristics are summarized in table 1. The majority of patients were male (88%) and mean age was 49 years (+/- 7 SD). Three patients were cirrhotic. One patient dropped out shortly after inclusion because of a newly diagnosed hepatocellular carcinoma (HCC), and **seven patients completed at least 16 weeks of therapy**. All patients were under concomitant therapy with nucleoside/nucleotide analogues. None had a concomitant interferon treatment, mostly due to patients' reticence or contraindications. A majority of patients had already completed at least one course of interferon therapy in the past.

ALT declined in a majority of patients during treatment with BLV. Mean ALT values before treatment (baseline) were 78 U/l (+/- 53 SD) and declined to 39 U/l (+/- 21 SD) after 16 weeks of therapy. The coefficient of fixed effects was -0.09 according to our mixed effect model ($p<0.05$), which means that the estimated reduction in ALT was 9% between each consultation. During therapy, **HDV-RNA dropped quickly in all patients except for one**. Mean HDV-RNA was 10,902,457 cop/mL (+/- 12,741,700 SD) at baseline and dropped to 3,740,569 cop/mL at week 16 (+/- 9,253,452 SD). The coefficient of fixed effects was -0.55 according to our model, indicating an estimated reduction in HDV-RNA value of 55% between each consultation ($p<0.05$). One patient showed no significant biochemical or viral response and was discontinued at week 16 (Patient 3). Evolution of ALT and HDV-RNA levels during treatment with bulevirtide are shown in tables 3 and 4, as well as figures 1 and 2, respectively.

There were **no patient-reported adverse events**. We observed no relevant lab abnormalities during treatment besides an asymptomatic elevation of bile acids (table 2).

Patient	Age at baseline	Sex	Cirrhosis	Baseline Thrombocytes (/nl)	Previous Interferon therapy	Nucleotide/ nucleoside therapy
1	50	male	no	258	yes	ETV
2	43	female	no	127	yes	TDF
3	53	male	no	97	yes	TDF
4	52	male	no	168	no	TDF
5	41	male	no	180	yes	TDF
6	46	male	yes	183	no	TDF
7	44	male	yes	54	yes	ETV
8	62	male	yes	66	no	ETV

Table 1: Baseline characteristics
ETV: Entecavir; TDF: Tenofovir Disoproxil Fumarate
Patient 8 dropped out 14 days after inclusion because of a newly diagnosed HCC

Patient	Baseline bile acids (µmol/L)	Week 4 bile acids (µmol/L)	Week 8 bile acids (µmol/L)	Week 12 bile acids (µmol/L)	Week 16 bile acids (µmol/L)
1	10.3	11.1	28.5	10.7	12.6
2	4	28	13.2	50.4	107.1
3	2	45.8	29.3	n.a.	65.7
4	7.1	4.1	7.9	9.5	n.a.
5	16.3	58	312	393.2	n.a.
6	n.a.	31	26	46.7	24.2
7	27	125	104	52.2	117.1

Table 2: Evolution of bile acids during treatment with BLV
n.a.: not available

Patient	Baseline ALT (U/L)	Week 4 ALT (U/L)	Week 8 ALT (U/L)	Week 12 ALT (U/L)	Week 16 ALT (U/L)
1	19	14	19	16	18
2	22	19	21	18	20
3	65	69	66	73	79
4	173	58	45	45	35
5	89	68	46	39	41
6	74	102	66	56	49
7	107	73	69	65	32

Table 3: ALT levels during the first 16 weeks of BLV therapy

Patient	Baseline HDV-RNA (cop/mL)	Week 4 HDV-RNA (cop/mL)	Week 8 HDV-RNA (cop/mL)	Week 12 HDV-RNA (cop/mL)	Week 16 HDV-RNA (cop/mL)
1	13,200	non detectable	non detectable	<3,000	<3,000
2	541,000	non detectable	non detectable	<3,000	5,380
3	>24,50,0000	6,240,000	>24,500,000	>24,500,000	>24,500,000
4	>24,500,000	5,030,000	1,150,000	255,000	665,000*
5	>24,500,000	>24,500,000	1,980,000	1,060,000	980,000
6	2,260,000	249,000	118,000	29,500	27,600
7	<3,000	5,230	<3,000	n.a.	<3,000

Table 4: HDV-RNA levels during the first 16 weeks of BLV therapy
** HDV-RNA for this patient was not available at week 16 but at week 20*

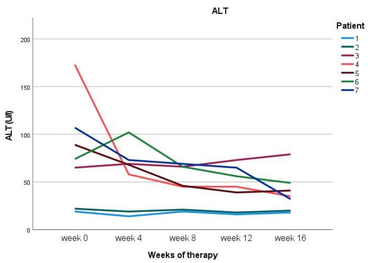

Figure 1: ALT levels during the first 16 weeks of BLV therapy

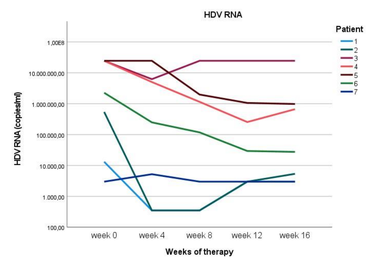

Figure 2: HDV RNA levels during the first 16 weeks of BLV therapy

Note: In our lab the linear range for measurement of HDV RNA ranges from 3,000 to 24.5 million copies/mL. In order to measure trends of viral load we considered values over 24.5 million copies/mL as equivalent to 24.5 million cop/mL and values under 3,000 to be equivalent to 3,000 cop/mL. Detection limit in our lab is 350 cop/mL.

4 Conclusions

These are the first real life data on bulevirtide therapy in Germany. Overall, we observed a **favorable safety profile** as well as a **marked biochemical and virological response** in the majority of our patients. However, many questions remain open regarding therapy with bulevirtide. The optimal duration of treatment is not known and there is no clear recommendation concerning this issue, which is particularly relevant when considering the relatively high costs of treatment (currently around 13.000 Euro per month in Germany). We currently have no data on the long-term effect of bulevirtide on the development of cirrhosis and hepatocellular carcinoma. Middle- and long-term data are needed to evaluate the impact of bulevirtide treatment on clinical endpoints in hepatitis delta patients.

5 References

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