MEDIZINISCHE UNIVERSITÄT WIEN

RESPONSE GUIDED LONG-TERM TREATMENT OF CHRONIC HEPATITIS D PATIENTS WITH BULEVIRTIDE – RESULTS OF A "REAL WORLD" STUDY

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BACKGROUND

Infection with hepatitis D Virus (HDV) causes progression to cirrhosis and hepatocellular carcinoma. HDV relies on hepatitis B virus (HBV), in particular on HBV surface antigen (HBsAg) to form infectious HDV particles. No effective treatment is available. Pegylated interferon alpha (PEGIFN) achieves sustained suppression of HDV replication only in 25% of patients. Nucleos(t)ide analogs (NUC's) are ineffective against HDV. The HBV entry Inhibitor Bulevirtide (BLV) is a synthetic N-acylated preS1 lipopeptide that blocks the sodium/bile acid cotransporter (NTCP), the receptor responsible for the entry of HBV and HDV into hepatocytes for hepatitis D.

METHODS

MyrPharma (Leipzig/Germany) provided BLV in a compassionate use program until 8/2020, and thereafter was prescribed through the Austrian health insurance. HDV-RNA was determined by PCR (according le Gal et.al, J.Clin Microbiol 2005; LLQ:100 copies/mL). BLV dose and treatment duration was at the discretion of the investigator. It is planned to terminate treatment after HDV-RNA being undetectable for 6 months.

Definition of Response pattern:.

Patients were classified as responder (≥2log drop of HDV-RNA within 24 weeks followed by further decline), partial responder (≥2log drop within 24 weeks and no further decline), non-responder (<2log drop of HDV-RNA within 24 weeks).

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Patient characteristics:

22 received BLV (2mg/d in 15; 10 mg/day in 2). In 15 patients (84.6%), BLV was combined with NUC's (n=3 ETV, n=10 TDF, n=2 TAF) Prior to BLV treatment 13 patients received one or several courses of PEGIFN therapy without success.

Response pattern:.

Patients were classified as responder (≥2log drop of HDV-RNA within 24 weeks followed by further decline), partial responder (≥2log drop within 24 weeks and no further decline), non-responder (<2log drop of HDV-RNA within 24 weeks).

Treatment outcomes:

21 patients completed at least ≥24 weeks of BLV treatment (range: 24-130 weeks), one dropped out at week 8.

10 patients were BLV responders. 4 patients achieved long-term HDV-RNA suppression for ≥6 months on BLV therapy (Fig.1). In 2 patients treatment was terminated because they were HDV-RNA negative for > 36 weeks. Details of patient #1 were published in detail. Treatment of #9 was terminated at week 63. HDV-RNA was became detectable again in both after 4 and 60 weeks of follow up, respectively. One patient underwent liver transplantation at week 25 and one was lost to follow up after week 26. Thus, 7 are still on BLV treatment.

Seven patients were nonresponders. In 4 PEGIFN (Fig.2; 90 µg/week in #2, #6 and 180 µg/week in #10, was added, all are still on treatment. 3 patients terminated treatment; 2 due to noncompliance (#5 and #11) and #14 underwent liver transplantation at week 25

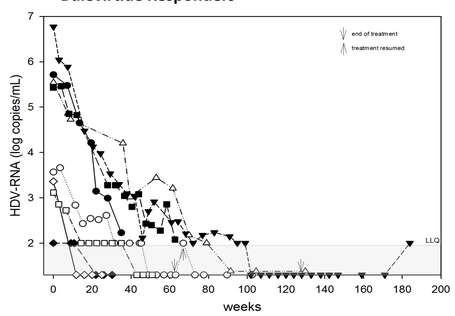
Cirrhotic patients

	P2	P4	P6	P7	P9	P10	P11	P12	P13	P14	P17	P18	P21	P22
Sex/ Age (a)	M/68	F/46	F/67	M/52	M/51	F/37	M/42	F/45	M/66	F68	F36	M/37	F/50	M59
Previous IFN	yes	yes	yes	yes	yes	yes	no	no	yes	yes	no	yes	yes	yes
HDV-RNA (copies/mL)	2.8 x10^6	2.1 x10^6	1.6 x10^5	7.1 x10^7	3.7 x10^3	2.7 x10^5	3.1 x10^4	1.2 x10^4	5.8 x10^3	8.2 x10^5	1.0 x10^2	1.6 x10^6	4.3 x10^5	26879
HBeAg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg	neg			neg
HBV-DNA (IU/mL)	<20	neg	<20	neg	neg	63	<20	neg	neg	neg	neg	neg	347	neg
HBsAg, quant	3142	9377	420	1229	1663		13649	181	44,6	2090	2266	2183	1161	4673
VCTE-LSM (kPa)	26.3	17.2	10.2	-	35.8	-	22.7	18.6	7.5	-	24	48	19.4	-
Bilirubin(mg/dL)	1.38	0.52	0.35	0.49	0.95	1.2	1.37	1.12	1.35	1.54	0.65	0.8	1.6	1.24
Albumin (g/dL)	34.4	31.0	44.8	44.1	46.1	43.0	38.1	41.8	39.9	33.9	49.9	36.7	32.5	41.9
INR	1.3	1.4	1.0	1.0	1.2	1.2	1.2	1.0	1.4	1.7	1.2	2.4	1.3	1.3
Platelets (G/L)	77	98	131	166	84	129	109	29	90	63	85	78	53	101
AST (IU/L)	55	93	64	21	68	48	87	35	36	94	24	56	315	86
ALT (IU/L)	63	80	75	25	125	56	115	35	44	69	24	73	307	132
GGT (IU/L)	30	52	43	37	98	31	177	16	26	48	30			88
Concomitant NUC therapy	ETV	ETV	TDF	TDF	ETV	TAF	TDF	no	TDF	TAF	TDF	TDF	TDF	TDF

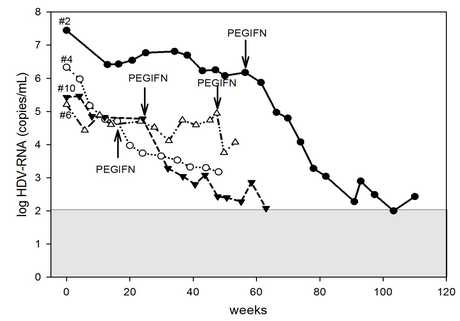
noncirrhotic patients

	P1	P3	P5	P8	P15	P16	P19	P20
Sex/ Age (a)	F/66	F/42	M/42	F/29	F36	F39	M/39	M/36
Previous IFN	yes	yes	yes	yes	yes	yes	yes	yes
HDV-RNA (copies/mL)	5.9 x10^6	5.2 x10^5	9.5 x10^4	4.3 x10^5	1.1 x10^6	2.3 x10^3	8.4 x10^3	8.3 x10^3
HBeAg	neg	pos	neg	pos	neg	neg		
HBV-DNA (IU/mL)	21	<20	neg	<20	neg	<20	neg	215
HBsAg, quant	9780	11825	1090	17326	5890	3643	19985	7321
VCTE-LSM (kPa)	-	9.1	7.4	5.5	7	9.5	11.8	1.7
Bilirubin(mg/dL)	0.36	0.47	0.52	0.5	0.28	0.65	0.7	0.8
Albumin (g/dL)	41.3	45.6	44.0	35.6	43.0	45.6	44.5	46.6
INR	1.0	1.0	1.0	1.2	1.1	1.3	1.1	1.1
Platelets (G/L)	216	251	162	288	257	206	62	74
AST (IU/L)	111	76	68	53	51	203	51	40
ALT (IU/L)	224	91	207	42	59	341	54	63
GGT (IU/L)	44	64	86	16	32	58		
Concomitant NUC therapy	TDF	TDF	TDF	no	TDF	TDF	TDF	TDF

Bulevirtide Responders

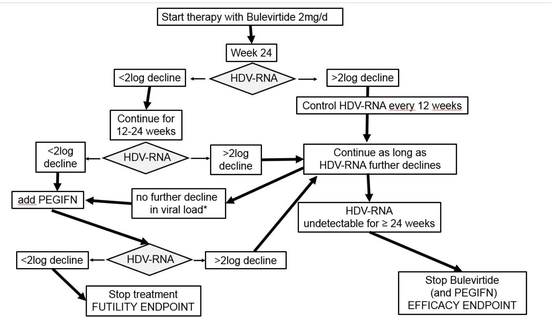


Addition of Peginterferon in Bulevirtide-Nonresponders



CONCLUSIONS

- BLV is an effective antiviral agent in hepatitis
- To eradicate HDV long-term treatment is needed
- We propose aA response guided approach is recommended, Proposal: :



Proposed treatment algorhytm