Ongoing analysis of virologic control / functional cure of HBV and HDV infection following REP 2139-Ca and pegylated interferon alpha-2a therapy in patients with chronic HBV / HDV co-infection: 3.5-year follow-up results from the REP 301-LTF study

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AASLD THE LIVER MEETING® NOVEMBER 8-12 2019 BOSTON

INTRODUCTION

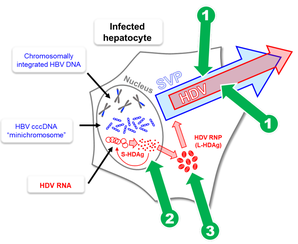
REP 2139 is a nucleic acid polymer which blocks the assembly / secretion of HBV subviral particles[1] and additionally binds to the small and large forms of HDAg[2], driving multiple antiviral mechanisms against HDV infection (see Fig. 1). In the previous REP 301 study (NCT02233075)[3] combination therapy with REP 2139-Ca and pegIFN in HBV/HDV co-infection was well tolerated and achieved > 5 log_{10} reduction in HDV RNA in 12/12 patients and HDV RNA target not detected in 11/12 patients. Additionally, 9/12 patients achieved HBsAg reduction > 1 log_{10} from baseline and 5/12 patients achieved HBsAg loss. During the initial 1-year follow-up in the REP 301 and REP 301-LTF (NCT02876419)[3] studies 7/12 and 5/12 patients had undetectable HDV DNA and HBsAg respectively with normalization of liver function and reversal of liver inflammation / fibrosis.

Figure 1. Antiviral effects of REP 2139:

(1) Inhibition of HBV SVP assembly / secretion and HDV envelopment.

(2) Potential inhibition of HDV RNA synthesis via interaction with S-HDAg.

(3) Potential inhibition of HDV RNP formation via interaction with L-HDAg.



AIM

To characterize the long term stability of the control of HBV and HDV infection and normalization of liver function in participants receiving REP 2139-Ca and pegIFN in the REP 301 study.

MATERIAL & METHODS

REP 301 patients (see Table 1) completing therapy were enrolled in the REP 301-LTF trial (NCT02876419). Patients are followed every 6 months for a period of 3 years (for a total of 3.5 years of treatment-free follow up including 24 weeks follow-up in the REP 301 study). HDV RNA, HBV DNA, HBsAg and anti-HBs are followed every 6 months using standard assays (Robogene MK II RT-PCR, Abbott RealTime HBV, Abbott Architect). Median hepatic stiffness is evaluated by Fibroscan.

Table 1. Pre-treatment demographics of participants enrolled in the REP 301 / REP 301-LTF studies.

Patient	Age	Sex	ALT (U/L)	Median Hepatic Stiffness (kPa)	HBsAg (IU/mL)	HBV DNA (IU/mL)	HBV RNA (log copies/mL)	HBcrAg (log U/mL)	HDV RNA (IU/mL)	Duration of HDV infection prior to treatment
001-01	33	F	188	8.4	13988	< 10	TND	< LLOD	394000	1 year, 5 months
001-02	29	F	98	7.7	27264	<10	TND	< LLOD	47100000	3 years, 6 months
001-03	40	M	53	14.8	28261	< 10	TND	< LLOD	697000	18 years
001-06	37	M	95	6.8	17511	726	TND	4.1	5490000	12 years
001-09	22	M	85	12.0	16426	104	1.73	4.4	211000	4 years, 7 months
001-11	35	M	200	9.6	12382	<10	TND	3.2	12100000	9 years
001-14	32	M	143	11.6	20869	<10	TND	< LLOD	23000000	6 years, 1 month
001-17	34	M	62	9.5	8314	350	TND	< LLOD	1690000	10 months
001-20	44	F	29	8.8	13430	<10	TND	4.5	27400	12 years
001-22	36	M	101	11.9	7836	16	2.22	5	1090000	1 year, 6 months
001-24	39	M	160	7.8	20473	<10	TND	2.8	1890000	4 years, 10 months
001-26	39	M	85	30.7	5854	256	TND	4.5	3760000	9 years

Table derived from (3). All patients were HDV genotype 1, HBeAg negative and anti-HBe positive.
Patient 01-014 was excluded from enrollment in the REP 301-LTF study as therapy was terminated early in this patient[3]. Participants where HBsAg is likely derived entirely from integrated HBV DNA are indicated in green.

RESULTS

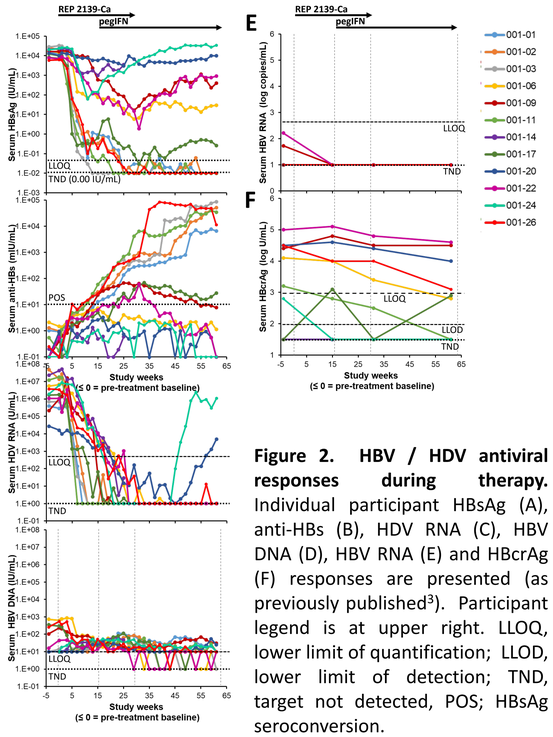


Figure 2. HBV / HDV antiviral responses during therapy. Individual participant HBsAg (A), anti-HBs (B), HDV RNA (C), HBV DNA (D), HBV RNA (E) and HBcrAg (F) responses are presented (as previously published[3]). Participant legend is at upper right. LLOQ, lower limit of quantification; LLOD, lower limit of detection; TND, target not detected, POS; HBsAg seroconversion.

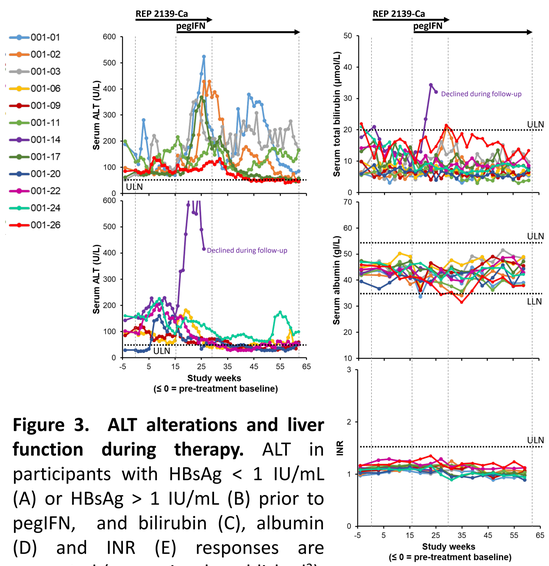


Figure 3. ALT alterations and liver function during therapy. ALT in participants with HBsAg < 1 IU/mL (A) or HBsAg > 1 IU/mL (B) prior to pegIFN, and bilirubin (C), albumin (D) and INR (E) responses are presented (as previously published[3]). Participant legend is at upper left. ULN, upper limit of normal; LLN, lower limit of normal.

Table 2. Individual response to treatment and outcome at latest follow-up

Patient (follow-up completed)	Parameter	Baseline	EOT	Last Follow-up
001-01 (3.5 years)	HBsAg (IU/mL)	13988	TND	0.83
	anti-HBs (mIU/mL)	1.03	6633	86
	HBV DNA (IU/mL)	< LLOQ	<LLOQ	**TND**
	HDV RNA (IU/mL)	**394000**	**TND**	**TND**
	ALT (U/L)	188	80	24
	AST (U/L)	160	111	25
	Med. Hep. Stiffness (kPa)	8.4	17.1	7.5
001-02 (3.5 years)	HBsAg (IU/mL)	27264	TND	**TND**
	anti-HBs (mIU/mL)	1.29	51970	172
	HBV DNA (IU/mL)	<LLOQ	TND	**TND**
	HDV RNA (IU/mL)	47100000	TND	**TND**
	ALT (U/L)	98	53	26
	AST (U/L)	64	61	27
	Med. Hep. Stiffness (kPa)	7.7	9.9	5.1
001-03 (3.5 years)	HBsAg (IU/mL)	28261	TND	**TND**
	anti-HBs (mIU/mL)	<0.1	86532	612
	HBV DNA (IU/mL)	<LLOQ	TND	**TND**
	HDV RNA (IU/mL)	697000	TND	**TND**
	ALT (U/L)	53	191	25
	AST (U/L)	36	129	29
	Med. Hep. Stiffness (kPa)	14.8	17.1	10.6
001-06 (3.5 years)	HBsAg (IU/mL)	17511	29.7	**TND**
	anti-HBs (mIU/mL)	2.1	1.13	7.6
	HBV DNA (IU/mL)	726	<LLOQ	**TND**
	HDV RNA (IU/mL)	5490000	TND	**TND**
	ALT (U/L)	95	53	14
	AST (U/L)	54	57	26
	Med. Hep. Stiffness (kPa)	6.8	7.1	6.1
001-09 (3.5 years)	HBsAg (IU/mL)	16426	399	8686
	anti-HBs (mIU/mL)	<0.1	7.76	<0.1
	HBV DNA (IU/mL)	104	31	546
	HDV RNA (IU/mL)	211000	TND	1580
	ALT (U/L)	85	34	75
	AST (U/L)	55	29	47
	Med. Hep. Stiffness (kPa)	12	12	15.4
001-11 (3.5 years)	HBsAg (IU/mL)	12382	<LLOQ	1596
	anti-HBs (mIU/mL)	0.55	34749	0.38
	HBV DNA (IU/mL)	<LLOQ	<LLOQ	13
	HDV RNA (IU/mL)	12100000	TND	**TND**
	ALT (U/L)	200	133	27
	AST (U/L)	85	100	25
	Med. Hep. Stiffness (kPa)	9.6	10.3	6.6
001-17 (3.5 years)	HBsAg (IU/mL)	8314	0.26	5221
	anti-HBs (mIU/mL)	<0.1	28	0.22
	HBV DNA (IU/mL)	350	<LLOQ	569
	HDV RNA (IU/mL)	1690000	TND	**TND**
	ALT (U/L)	62	46	42
	AST (U/L)	44	45	27
	Med. Hep. Stiffness (kPa)	9.5	9.8	
001-20 (3.5 years)	HBsAg (IU/mL)	13430	9964	22503
	anti-HBs (mIU/mL)	<0.1	<0.1	<0.1
	HBV DNA (IU/mL)	<LLOQ	25	TND
	HDV RNA (IU/mL)	27400	4920	11800
	ALT (U/L)	29	47	45
	AST (U/L)	27	50	20
	Med. Hep. Stiffness (kPa)	8.8	10.2	9
001-22 (3.5 years)	HBsAg (IU/mL)	7836	917	1341
	anti-HBs (mIU/mL)	<0.1	<0.1	<0.1
	HBV DNA (IU/mL)	16	<LLOQ	10
	HDV RNA (IU/mL)	1090000	TND	2310
	ALT (U/L)	101	58	95
	AST (U/L)	78	42	56
	Med. Hep. Stiffness (kPa)	11.9	11.8	7.6
001-24 (3.5 years)	HBsAg (IU/mL)	20473	34201	25184
	anti-HBs (mIU/mL)	<0.1	<0.1	<0.1
	HBV DNA (IU/mL)	<LLOQ	<LLOQ	37
	HDV RNA (IU/mL)	1890000	1090000	906000
	ALT (U/L)	160	97	193
	AST (U/L)	88	82	108
	Med. Hep. Stiffness (kPa)	7.8	8.2	10.6
001-26 (3 years)	HBsAg (IU/mL)	5854	TND	**TND**
	anti-HBs (mIU/mL)	0.25	11291	3034
	HBV DNA (IU/mL)	256	<LLOQ	**TND**
	HDV RNA (IU/mL)	3760000	TND	**TND**
	ALT (U/L)	85	51	38
	AST (U/L)	61	65	35
	Med. Hep. Stiffness (kPa)	30.7	27	24.3

HBsAg < 1IU/mL, HBsAg seroconversion, HBV DNA < LLOQ, HDV RNA TND achieved during therapy
HBsAg reduction > 1 log from baseline but > 1 IU/mL
HBsAg reduction < 1 log from baseline
Virologic control / functional cure of HBV infection when HDV RNA remains TND
Numbers in bold indicate functional remission of HBV (HBV DNA < LLOQ and normal liver enzymes) or HDV infection (HDV RNA TND) and HBsAg < LLOQ
TND = target not detected, LLOQ = lower limit of quantification
HDV RNA TND was achieved during REP 2139 therapy but rebounded following transition to pegIFN monotherapy

SUMMARY

Table 3. Maintenance of clinical, HBsAg and HDV RNA responses

Completed treatment and 3-3.5 years of follow-up		11
Clinical response	Normal ALT	8/11 (73%)
	Normal / declining liver median stiffness	7/11 (64%)
HBsAg response	< 1 IU/ml	6/11 (55%)
	≤ LLOQ (0.05 IU/mL)	5/11 (42%)
	Seroconversion	4/11 (36%)
HDV RNA response	**> 2 log_{10} reduction from baseline**	**9/11 (82%)***
	TND	**7/11 (64%)**

***2 participants maintaining 2.67 and 2.12 log_{10} reduction from baseline did not maintain normal liver function during follow-up (see 001-09 and 001-22 in Table 2).**

Table 4. HBV outcomes in participants with persistent HDV RNA negativity

Functional cure of HDV at 3-3.5 years of follow-up (HDV RNA TND, ALT normal)		7
HBV DNA response	≤ 2000 IU/mL	7/7 (100%)
	Target not detected (TND)	5/7 (71%)
HBV virologic response	Virologic control HBV (HBV DNA ≤ 2000 IU/mL, normal ALT)	3/7 (43%)
	Functional cure HBV (HBsAg < LLOQ, HBV DNA TND, normal ALT)	4/7 (57%)
	HBV clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	**7/7 (100%)**

CONCLUSIONS

1. **Combination therapy with REP 2139 and pegIFN achieves high rates of HBsAg loss and seroconversion accompanied by HBV RNA, HBcrAg and HDV RNA loss during therapy.**
2. **Stronger transaminase flares are associated with introduction of pegIFN but only in participants with HBsAg < 1 IU/mL .**
3. **Strong transaminase flares are correlated with better therapeutic outcomes.**
4. **Functional cure of HDV infection (HDV RNA TND, normal ALT) off therapy is achieved in 64% of participants and persists for at least 3.5 years.**
5. **All participants with functional cure of HDV have either virologic control or functional cure of HBV.**
6. **Outcomes are expected to significantly improve with the triple combination regimen (48 weeks of TDF + pegIFN + REP 2139-Mg) used in the REP 401 study.**

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DISCLOSURES

MB and AV are employees of and shareholders in Replicor. The Institute for Virology, University Hospital Essen received support from Replicor for the virologic testing. All other authors have no conflicts of interest to declare.

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