One year follow-up and HBV RNA / HBcrAg analysis in the REP 301 Trial: REP 2139 and pegylated interferon alpha-2a in Caucasian patients with chronic HBV / HDV co-infection

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INTRODUCTION

HBV/HDV co-infection represents a significant unmet medical need, causes rapid progression of liver disease and has no approved therapy. In the REP 301 trial (NCT02233075), REP 2139 monotherapy was followed by add-on pegylated interferon alpha 2a (peg-INF) in patients with HBeAg negative chronic HBV/HDV co-infection. At 24 weeks of follow-up, 7/12 patients remained HDV RNA negative, 6 also maintained HBV DNA suppression (<10 IU/mL) and 5 maintained HBsAg loss (0.00 IU/mL). A 3-year follow-up is underway (REP 301-LTF, NCT02876419). The initial 1 year follow-up data and HBV RNA / HBcrAg analysis are presented.

AIMS

- To characterize the long term effects of NAP-based combination therapy in patients with chronic HBV / HDV co-infection.
- To examine changes in HBV RNA and HBcrAg in the REP 301 trial.

METHODS

REP 301 patients (see Table 1) completing therapy were enrolled in the REP 301-LTF trial. Patients will be followed every 6 months for a period of 3 years. HDV RNA, HBV DNA, HBsAg and anti-HBs are followed every 6 months using standard assays (Robogene RT-PCR, Abbott RealTime HBV, Abbott Architect). HBV RNA analysis and HBcrAg (Fujirebio Lumipulse®) was conducted on frozen serum samples at DDL Diagnostic Laboratory (Rijswijk, The Netherlands).

RESULTS

- At baseline, all patients had substantial serum HBsAg and HDV RNA (Table 1).
- Four patients were HBV DNA < LLOQ, HBV RNA and HBcrAg negative (Table 1, green boxes).
- During REP 2139 monotherapy, HBcrAg reductions were minimal or absent in all HBcrAg positive patients despite multilog HBsAg declines (Figure 1).
- With add-on peg-IFN therapy, HBV RNA became negative in 2/2 HBV RNA positive patients (Figure 1, patients 9, 22) and HBcrAg had declined or became undetectable in 3 HBcrAg positive patients (Figure 1, patients 6, 11, 26).
- All patients with HBsAg, HBV DNA and HBV RNA loss at 24 weeks follow-up were also HBcrAg and HBV RNA negative.
- One year follow-up demonstrates that at least 4/5 patients with HBsAg loss at 24 weeks follow-up are maintaining HBsAg, HDV RNA and HBV DNA loss at 1 year post therapy.
- In 2 patients, persistently lowered HBsAg during follow-up was associated with normalization of liver transaminases despite rebound in serum HBV or HDV viremia (Table 2, green boxes).

Table 1. Pre-treatment patient characteristics in the REP 301 301-LTF trials

Patient	Age	Sex	ALT (U/L)	Fibrosis score (metavir[1])	HBeAg	Anti-HBe	HBsAg (IU/mL)	HBV DNA (IU/mL)	HBV RNA (log copies/mL)	HBcrAg (log U/mL)	HDV RNA (IU/mL)[2]
001-01	33	F	188	F2-F3	negative	positive	13988	< 10	TND	< LLOD	394000
001-02	29	F	98	F1-F2	negative	positive	27264	<10	TND	< LLOD	47100000
001-03	40	M	53	F4	negative	positive	28261	< 10	TND	< LLOD	697000
001-06	37	M	95	F0-F1	negative	positive	17511	726	TND	4.1	5490000
001-09	22	M	85	F3-F4	negative	positive	16426	104	1.73	4.4	211000
001-11	35	M	200	F2-F3	negative	positive	12382	<10	TND	3.2	12100000
001-14	32	M	143	F3	negative	positive	20869	<10	TND	< LLOD	23000000
001-17	34	M	62	F2-F3	negative	positive	8314	350	TND	< LLOD	1690000
001-20	44	F	29	F2-F3	negative	positive	13430	<10	TND	4.5	27400
001-22	36	M	101	F3-F4	negative	positive	7836	16	2.22	5	1090000
001-24	39	M	160	F2	negative	positive	20473	<10*	TND	2.8	1890000
001-26	39	M	85	F4	negative	positive	5854	256	TND	4.5	3760000

1. As determined by Fibroscan.
2. All patients were HDV RNA genotype 1.

TND = target not detected, LLOD = lower limit of detection (2 log U/mL for HBcrAg).

Table 2. Follow up responses in the REP 301 / 301-LTF trials.

Patient	Follow-up response (virologic)			Follow-up (Liver function)				
	HBV functional control[1]	log HBsAg reduction (follow up vs baseline)	HDV functional control[2]	LFT	Baseline	EOT	FW24	FW 1Y
001-01	YES	6.14	YES	ALT	188	80	33	37
				AST	160	111	29	29
001-02	YES	6.43	YES	ALT	98	53	21	24
				AST	64	61	23	26
001-03	YES	6.45	YES	ALT	53	191	20	25
				AST	36	129	24	40
001-06	NO	2.07	YES	ALT	95	53	17	21
				AST	54	57	24	30
001-09	NO (DNA rebound)	0.39	NO	ALT	85	34	56	71
				AST	55	29	38	44
001-11	YES	5.61	YES	ALT	200	133	57	29
				AST	85	100	46	27
001-14	NO	0.17	NO	ALT	143	415	172	NE[3]
				AST	64	258	128	NE[3]
001-17	NO	0.24	YES	ALT	62	46	29	42
				AST	44	45	30	35
001-20	NO	0.95	NO	ALT	29	47	53	37
				AST	27	50	45	33
001-22	NO	0.78	NO	ALT	101	58	33	29
				AST	78	42	28	27
001-24	NO	-0.16	NO	ALT	160	97	191	NA
				AST	88	82	133	NA
001-26	YES	5.76	YES	ALT	85	51	46	NA
				AST	61	65	48	NA

1. HBsAg = 0.00 IU/mL, HBV DNA < 10IU/mL, HBV RNA target not detected, HBcrAg < LLOD
2. HDV RNA target not detected

NE = not enrolled. Patient 001-14 was withdrawn from treatment due to pegIFN induced DILI and not eligible for participation in the REP 301-LTF.
NA = not available – 1 year follow results are not yet available for these patients.

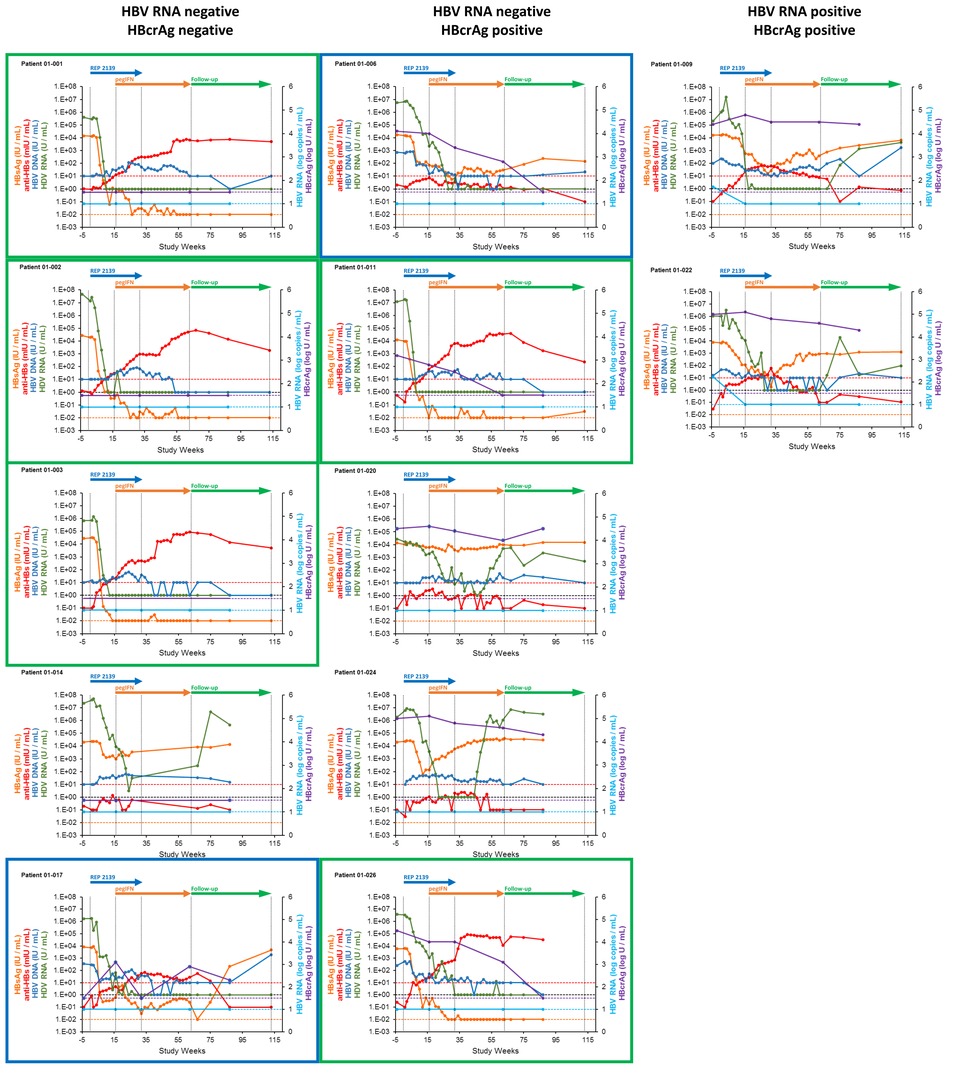

Figure 1. Individual patient virologic responses to combination therapy with REP 2139 and pegIFN in the REP 301 / 301-LTF protocols.
Individual tracings for HBsAg, anti-HBs, HBV DNA, HDV RNA, HBV RNA and HBcrAg presented for all 12 patients. Patients are grouped according to HBV RNA and HBcrAg reactivity. Patients exhibiting functional control of HBV and HDV are boxed in green. Patients exhibiting functional control of HDV only are boxed in blue. Dotted lines indicate either target not detected or < LLOQ / LLOD and are colour matched to their respective targets. For HBV DNA and HDV RNA, the dotted line for target not detected is indicated in black.

CONCLUSIONS

- **In patients with HBV / HDV co-infection, a significant proportion of serum HBsAg may be derived from integration and may be sufficient for HDV co-infection to persist.**
- **The selective effect of REP 2139 on serum HBsAg but not HBcrAg is consistent with the selective targeting of subviral particle release in cells harbouring infection or integration.**
- **One year follow-up data demonstrate that REP 2139 combined with peg-IFN establishes a stable and profound functional control of HBV and HDV infection in 5 / 12 patients and of HDV infection in 7 / 12 patients.**
- **Long term suppression of HBsAg may suggest elimination of hepatocytes with integrated HBsAg.**
- **Persistently lowered HBsAg after NAP therapy may have a therapeutic benefit for reduced liver inflammation, even in patients with residual active infection, increasing the overall benefit from NAP therapy.**

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DISCLOSURES

MB and AV are employees of and shareholders in Replicor Inc. The other authors have nothing to disclose.

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