Hepatitis delta virus (HDV) kinetics under the prenylation inhibitor lonafarnib suggest HDV-mediated suppression of HBV replication

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1. Background & Aims

- 15-20 million people worldwide are chronically infected with hepatitis D (HDV). Up to 80% of patients with HDV may develop cirrhosis within 5-10 years.
- Interferon-based therapy is unsatisfactory, <30% become HDV RNA negative and hepatitis B surface antigen (HBsAg) loss is rare [1-5]. Nucleos/tide analogues are ineffective [4].
- The prenylation inhibitor lonafarnib (LNF) is an oral, potent antiviral agent providing a breakthrough for the treatment of Hepatitis D [6].
- Analysis of HDV-specific antiviral treatment response kinetics may provide novel information about the interplay between HDV and hepatitis B virus (HBV).

2. Patients, Study Design & Kinetic Data

HDV RNA, HBV DNA, HBsAg and ALT kinetics data were obtained from a phase 2 study of 5 LNF-based treatments (LOnafarnib With Ritonavir in Hepatitis Delta Virus – 1, LOWR HDV-1 Study) (Table 1).

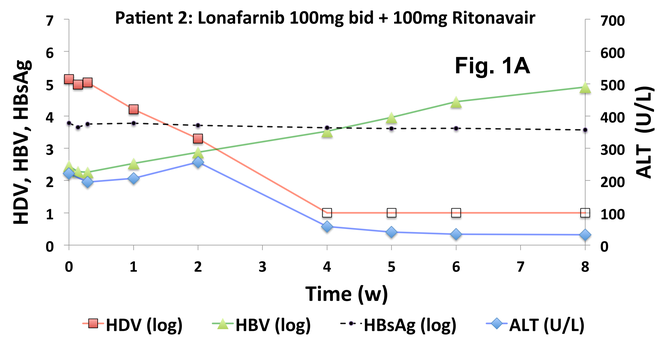
Table 1. Baseline characteristics

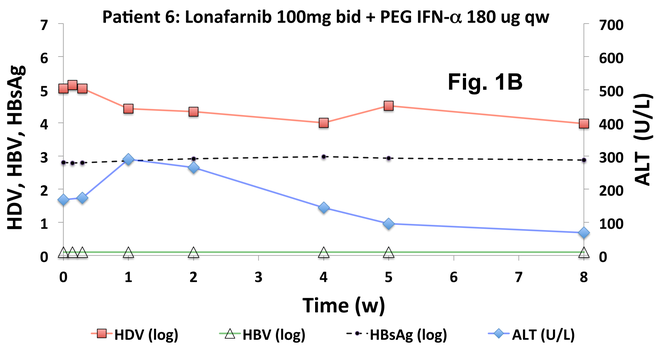
Pt	Rx Regimen [duration, weeks]	HBsAg (log IU/mL)	HDV RNA (log cp/mL)	HBV DNA (log IU/mL)	ALT (U/L)
1	LNF 100mg bid + ritonavir 100mg qd [8 wks]	4.28	6.00	1.97	84
2		3.79	5.00	2.53	189
3		4.07	6.68	4.11	71
4	LNF 100mg bid + PEG IFN-α 180 μg qw [8 wks]	3.84	6.08	2.18	143
5		3.73	4.18	BD	137
6		2.80	5.61	BD	164
7	LNF 100mg tid [5 wks]	3.54	4.74	2.97	70
8		4.00	6.88	3.20	42
9		4.36	4.81	1.53	22
10	LNF 200mg bid [12 wks]	3.90	4.11	3.32	90
11		3.65	6.54	0.10	43
12		3.57	4.11	2.26	206
13	LNF 300mg bid [12 wks]	2.75	3.00	2.52	65
14		4.02	3.51	3.51	138
15		4.11	5.81	6.11	47

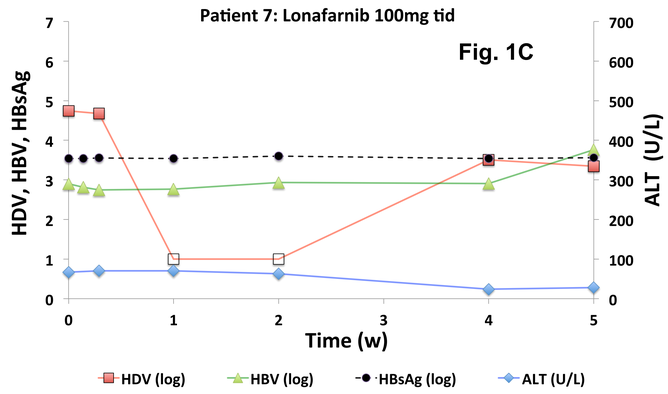
None of the patients received anti-HBV treatment with nucleos(t)ide analogues. Serum samples for kinetics analysis were obtained before treatment and on days 1, 2, 3, 7, 14 and then every 2 weeks until end of treatment (EOT).

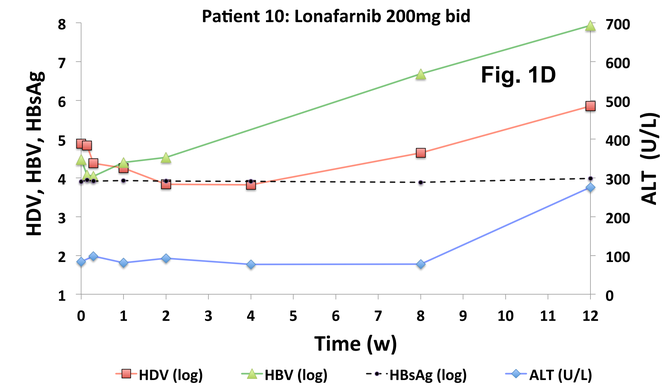
3. Results

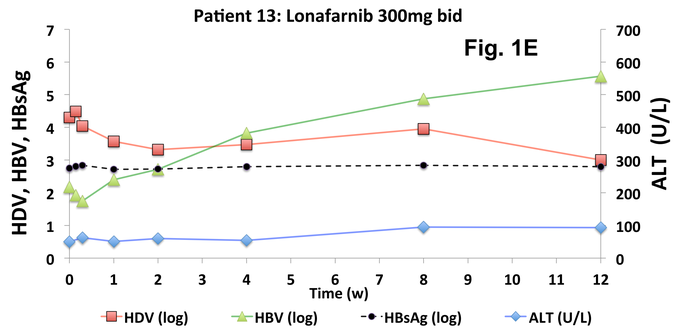
- The kinetics pattern of HDV RNA during LNF-based treatment consisted, in all patients, of two phases: a 1st rapid decline with median slope of 0.91 log/wk/mL [interquartile range (IQR):0.43], that lasted 1.5 wks [IQR:1,4], followed by an undetectable [n=1; Fig. 1A], slower 2nd decline phase [n=3; Fig. 1B], rebound [n=5; Figs. 1C and 1D], or plateau [n=6; Fig. 1E].
- HDV RNA rebounds were proportional to a decrease in LNF serum drug levels (attributed to GI intolerability / non-compliance)
- Patients who were treated with LNF 300 mg bid (Fig. 1E) or LNF 100 mg bid + ritonavir (Fig. 1A) had either 2nd phase decline or plateau.
- While in 7 patients (including all subjects treated with LNF + PEG IFN-α) HBV remained at pre-treatment levels, in 8 patients an increase in HBV was evident with a median increasing slope of 0.32 log/wk/mL [IQR:0.15].
- The median ALT level at EOT, 43 U/L [IQR:36], was significantly reduced from a median pre-treatment level of 82 U/L [IQR:118] (p=0.03).
- The rise in HBV DNA of up to 5 $\log_{10}$ IU/mL from pre-treatment level was not associated with a concomitant rise in ALT levels (p=0.8).
- There was a significant positive correlation between the reduction in HDV and ALT from baseline to EOT (r=0.55, p=0.03). HBsAg levels did not change during treatment (Fig. 1)











Open red squares and green triangles represent HDV RNA and HBV DNA measurements below detection.

Conclusions

- Treatment with LNF provides a novel window into the dynamics between HDV and HBV replication.
- The inverse relationship between HDV and HBV observed in about 67% of patients, who were LNF-treated without PEG IFN-α, is consistent with viral interference in which HDV suppresses HBV in co-infected patients.
- The decline in ALT levels in all but two patients combined with the re-emergence of HBV is consistent with LNF exerting a direct effect on blocking HDV replication/assembly rather than promoting the death of productively infected cells. This further supports the dominant role of HDV in liver injury in chronic HDV infection.
- HDV RNA rebounds were attributed to decreased LNF serum levels associated with poor GI tolerability. This is currently being addressed in an on-going Phase 2 LOWR HDV-2 study where lower LNF/ritonavir doses are associated with better GI tolerability, sustained drug levels and antiviral response.

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