understanding hepatitis delta virus and HBsAg kinetics during treatment with prenylation inhibitor lonafarnib via mathematical modeling

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1. Background & Aims
15-20 million people are infected worldwide with chronic hepatitis D (HDV). Up to 80% of patients with HDV may develop cirrhosis within 5-10 years. Interferon-based therapy is unsatisfactory, <30% achieve HDV clearance and become HDV RNA negative. Nucleos/tide analogues are ineffective. 14 chronically infected HDV patients were sequentially enrolled into 2 groups. We assume the target cell i.e., HBsAg-productive cell, count was constant and was measured on stored serum samples using the International Immunodiagnostic System (EUSA) with HBsAg standards from Alpha Diagnostics International.

2. Patients, Study Design & Kinetic Data
14 chronically infected HDV patients were sequentially enrolled into 2 groups in a phase 2a double-blinded, randomized, placebo-controlled study (Fig. 1 and Table 1). Patients received treatment for 28 days, followed by post-treatment monitoring for six months.

3. Dual Model Description
The kinetics of HDV and HBsAg during LNF therapy was modeled using our dual model (Fig. 2) for HDV and HBsAg kinetics during pegIFN therapy [7]. We simultaneously fitted the model to the log-scaled HDV viral loads and HBsAg levels, using a nonlinear mixed effect modeling approach. Population estimates and inter-individual variability (IVV) estimates were obtained using a maximum likelihood method implemented in NONMEM version 4.3.2.

4. HDV RNA & HBsAg Kinetics
- HDV remains at baseline levels (Fig. 3)
- Biphasic decline during therapy in all LNF-treated patients (Fig. 3)
- First rapid decline phase followed by a second slower (or plateau) phase (Table 2).
- First phase duration longer in Group 2 compared to Group 1 (Table 2).

5. Model Fits & Parameter Estimations
- Fitting the HDV and HBsAg dual model (Fig. 3) with measured HDV and HBsAg kinetics yielded excellent fit curves.
- The pretreatment serum HDV RNA and HBsAg levels were estimated as 5.97 (se=0.13) log IU/mL and 4.17 (se=0.12) log ng/mL, respectively.
- A short pharmacological delay of t0=0.73 (se=0.24) day, in which HDV remained at baseline levels, was not associated with LNF dose.
- The HDV clearance rate in blood, c, was estimated as 0.426 (se=0.04) d-1, corresponding to an HDV half-life in blood of 1.63 (se=0.15) days.
- LNF effectiveness in blocking HDV production was significantly (p<0.001) higher in Group 2 (se=0.952 (se=0.057)) than Group 1 (c=0.739 (se=0.05))

Table 2: HDV 1st and 2nd phase slopes and their transition time by segmented linear regression (SLR).

Parameter (unit) | Parameter description | Population value (se) | Inter-individual variability % (se)
---|---|---|---
\[ t_0 \] [d] | Pharmacological delay | 0.73 (0.24) | 66 (33)
Lnf2/3 [d] | HDV half-life in blood | 1.63 (0.07) | 16 (11)
\[ c^* \] | Group 1 Lona gift significantly in blocking HDV production | 0.739 (0.05) | 15 (3)
| Group 2 Lona gift significantly in blocking HDV production | 0.952 (0.057) | 15 (3)
V0 [log10 IU/mL] | Pre-treatment HDV viral load | 5.97 (0.13) | 7.5 (1.6)
H0 [log10 ng/mL] | Pre-treatment HBsAg level | 4.17 (0.12) | 9.5 (2.0)

The death/loss rate of productively HDV-infected cell was fixed to ν = 0.01 to account for the observed kinetics of both HDV and HBsAg. * c is significantly (p=0.0056) higher in Group 2 compared to Group 1.

Conclusions
- The observed stable HDV level at LNF treatment suggests that the productively HDV-infected cell number remained unchanged during this relatively short treatment period.
- The modeling analysis indicated a dose dependent effect of LNF in blocking HDV release with efficacies of 74% and 95% in the Groups 1 and 2, respectively. Moreover, the 95% efficacy of the 200 mg LNF dose was similar to recent estimates in patients treated with peg-IFN [7] (ε=96%) and was achieved much earlier with LNF (median 12.5 days) compared to pegIFN (median 25.2 days).
- A strikingly shorter delay was observed with LNF (t0=0.73 day) compared to HDV-infected patients treated with peg-IFN (t0=8.5 day).
- Frequent measurements under LNF therapy allowed for a refined estimate of HDV t1/2=1.6 day that was about 2-fold shorter than under peg-IFN (t1/2=2.9 day), and suggests a higher HDV production rate than recently estimated [7].
- This shorter \[ t_0 \] is reminiscent of the dual mechanism of action observed with an HCV NSSA inhibitor [8], which suggests that LNF might similarly have two mechanisms of action that result from inhibiting farnesylation of large delta antigen: one involving inhibition of HDV particle production, and a second resulting from increased retention of intracellular unprenylated LDHAg, which in turn can increase HDAg’s transdominant inhibitory effect on HDV RNA genome replication.
- Additional viral kinetic analyses based on these results and future studies should help enable determination of the optimal dose and duration needed to ensure proper eradication of those infected with HDV.

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