Pharmacokinetics and pharmacodynamics modeling of lonafarnib in patients with chronic hepatitis delta virus infection

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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% achieve hepatitis B surface antigen (HBsAg) loss and become HDV RNA negative [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 delta virus (HDV) and an opportunity to further characterize HDV dynamics during treatment [6]. Here, we used modeling to estimate the pharmacokinetic (PK), pharmacodynamics (PD) and viral kinetic (VK) parameters to further describe the interaction between the drug, host, and virus.

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 [6] (Fig. 1 and Table 1). Patients received treatment for 28 days, followed by post-treatment monitoring for six months.

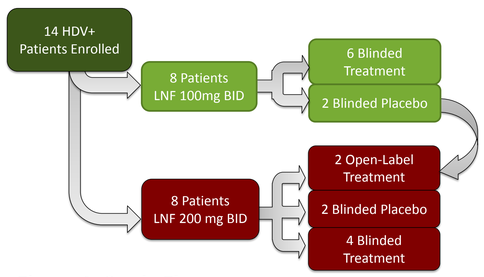

Figure 1: Study Flow.

Feature	Result
Males	71%
Median Age	38
Nucleoside Analogues	31%
Race	
Caucasian	43%
Asian	50%
African	7%
Median Baseline Histology	
Ishak Fibrosis	3

Table 1: Patient demographics.

Patients were treated with LNF 100 mg twice daily (bid) (Group 1) or 200 mg twice daily (bid) (Group 2) for 28 days. PK samples were collected at 0, 6, 12, 18, 24, 36, 48, 60, 72 h relative to the first dose; at 0, 0.25, 0.5, 1, 2, 4, 6, 12 h on day 14 (steady-state); and on days 21 and 28 (pre-dose). VK samples were collected at 0, 6, 12, 18 h relative to the first dose and on days 1, 1.5, 2, 3, 7, 14, 21, 28 (pre-dose). LNF concentration was measured by mass spectrometry. HDV RNA was measured RT-PCR with lower detection limit of 70 IU/mL.

3. PK/PD Model Description

LNF pharmacokinetic (PK) and HDV viral kinetic (VK) were modeled using the following:

- PK : 1-compartment model with lag-time, 1st order absorption (ka) and 1st order elimination (k)
- VK: standard biphasic model (Box 1)

$$\frac{dI}{dt} = \beta V T_0 - \delta I$$
$$\frac{dV}{dt} = p(1-\varepsilon(t))I - cV$$

Box 1. biphasic model.

I: infected cells that can produce HDV virion; *V*: HDV RNA level in blood. β: infectivity rate; *p*: HDV production rate, δ: infected cell loss rate; *c*: HDV clearance rate; $\varepsilon(t)$: LNF effectiveness (see Box 1).

We assume the target cell i.e., HBsAg-productive cell, count was constant during 28 days with lonafarnib treatment and equal to its pre-treatment steady-state value $T_0 = c\delta/\beta p$.

We modelled LNF PD according to the Emax model shown in Box 2.

$$\varepsilon(t) = \mathrm{Emax}\frac{C(t)^h}{EC_{50}^h + C(t)^h}$$

Box 2. Emax model.

where *C* is LNF concentration, EC_{50} LNF concentration leading to an effectiveness 50%, and *h* the Hill coefficient, which determines how steeply the effectiveness varies with drug concentration.

3. PK/PD Model Description (Continued)

Model simulations and sensitivity analysis: We simultaneously fit the model to the log-scaled serum HDV viral loads and LNF concentration levels, using a nonlinear mixed effect modeling approach. Population estimates and inter-patient variability (IPV) estimates were obtained using a maximum-likelihood method implemented in MONOLIX version 4.3.2. Individual parameters are empirical Bayes estimates.

4. Results

- The model fit well the observed data (Fig. 2).
- Model PK and PD parameter estimations are summarized in Table 2.
- Model parameters are accurately estimated with relative standard error (rse, i.e. (standard error)/(estimate), <30% for the population estimates and <50% for the IPV).

Table 2. Parameter estimates

Parameter [unit]	Parameter description	Population estimate (rse %)	Inter-Patient variability % (rse %)
t_0 [hr]	Pharmacological delay	0.56 (16)	52 (23)
ka[hr^{-1}]	LNF absorption rate	0.43 (28)	83 (27)
V [L]	Volume of distribution	223 (15)	49 (23)
ke [hr^{-1}]	Elimination rate	0.045 (13)	39 (25)
Emax	Maximal effectiveness	1.0 (1)	-**
EC50 [ng/mL]	LNF concentration leading to 50% of effectiveness	227 (26)	62 (23)
h	Hill factor	1.48 (7)	-
V_0 [log10 IU/mL]	Pre-treatment HDV viral load	7.88 (2)	5.7 (21)
δ [d^{-1}]	Infected cell loss rate	0.01 (FIXED)*	-
c [d^{-1}]	Free virus clearance rate	0.37 (10)	21 (48)

* The death/loss rate of productively HDV-infected cell was fixed to δ=0.01 to account for the observed kinetics of both HDV and HBsAg [6].

** The model with no IPV for *Emax*, *h* and δ provided the best fits. This implies that *Emax*, *h* and δ have the same value for all subjects

4. Results (Continued)

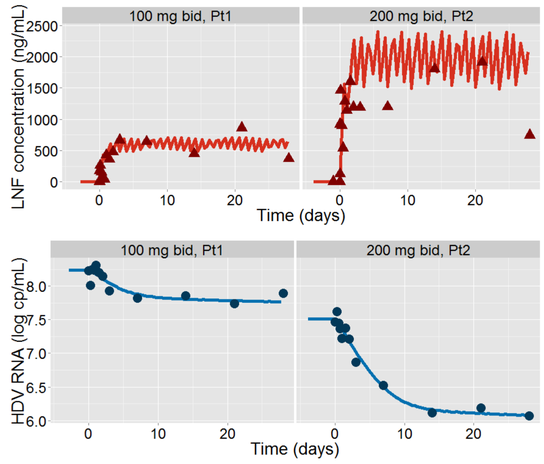

Figure 2: LNF PK (upper panel) and HDV VK fits (lower panels) during 100 mg (left panels) or 200 mg (right panels) bid of lonafarnib (LNF). Representative LNF PK (red) and HDV viral load (blue) observations are shown with dark triangles & dots, respectively. The best-fit curves are shown in red and blue for LNF PK and HDV viral load, respectively.

- From the population estimates, we predict that steady-state concentration is 860 and 1734 ng/mL for groups 1 and 2, respectively. This leads to an effectiveness of 87.7 and 95.2% inducing a viral decline of 0.91 and 1.32 log IU/mL for groups 1 and 2 respectively (Table 3).
- The model predicts that LNF concentrations of 1002 ng/mL and 5063 ng/mL achieve 90% and 99% efficacies in blocking HDV production, respectively.
- Figure 3 shows viral decline vs. LNF concentration and the dose effect.

Table 3. Predicted LNF steady-state and effectiveness

	Steady state concentration (ng/mL)	Drug effectiveness (%)	Viral load decline (log IU/mL)
Group 1 : 100 mg bid	860	87.7	0.91
Group 2 : 200 mg bid	1734	95.2	1.32

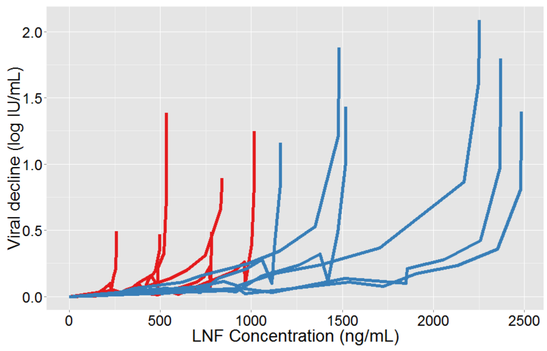

Figure 3: Predicted drug effect during 100 (red) or 200 (blue) mg bid of lonafarnib (LNF). Each patient is represented by a line showing the viral decline vs. drug concentration

5. Conclusions

- ❑ We provide the first insights into LNF PK and PD in chronically HDV-infected patients.
- ❑ Modeling results suggest that steady-state LNF concentration above 1002 ng/mL and 5063 ng/mL could achieve 90% and 99% efficacies in blocking HDV production, respectively.

6. References

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7. Acknowledgements

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8. Disclosures

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