The Prenylation Inhibitor Lonafarnib (LNF) Can Induce Post-Treatment Viral Clearance in Patients with Chronic Hepatitis Delta (CDH) Resulting in ALT Normalization and Regression of Fibrosis:

Summary of Observations from Individual Cases: Retreatment with Lonafarnib in a Subset of HDV-Infected Patients

C. YURDAYDIN[1*], R. IDILMAN[1], C. KALKAN[1], F. KARAKAYA[1], A. CALISKAN[1], O. KESKIN[1], E. YURDCU[1], S. Karatayli[1], A. M. Bozdayi[1], C. Koh[2], T. Heller[2], J. S. Glenn[3*]

Division of Gastroenterology, University of Ankara Medical School, Ankara, Turkey[1]; Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland[2]; Division of Gastroenterology and Hepatology, Stanford University School of Medicine[3]. *These authors share senior authorship.

1. Abstract

Background and Aims: CDH is the most severe form of viral hepatitis, with no adequate therapy. The prenylation inhibitor LNF is the first investigational agent targeted for hepatitis D virus (HDV). Here we report the post-treatment clearance and subsequent follow-up course in patients who were HDV-RNA positive following treatment with 12-24 weeks of LNF.

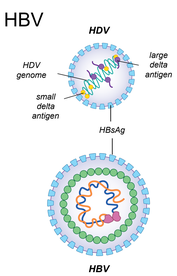
Methods: 27 patients were analyzed who had detectable end of treatment HDV-RNA after receiving LNF for 12-24 weeks in the LOWR HDV-1 and LOWR HDV-2 (LOnafarnib With Ritonavir for HDV–1 and 2) trials, and who were at least 24 weeks post-treatment. A post-treatment ALT flare was defined as elevation of ALT to >2x baseline (BL) level.

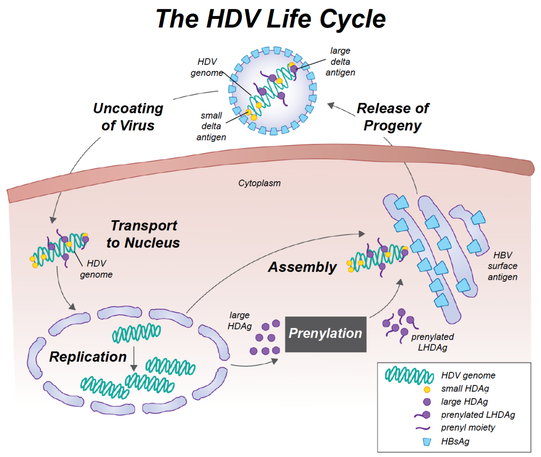
Results: Patients came from multiple LNF treatment cohorts: LNF 200 mg BID, 12 weeks; LNF 300 mg BID, 12 weeks; LNF 100 mg BID + RTV 50 mg BID, 12 weeks; LNF 75 mg BID + RTV 100 mg BID, 12 weeks, followed by addition of pegylated interferon alfa, 12 weeks; LNF 50 mg BID + RTV 100 mg BID, 24 weeks. Following treatment, 5 of 27 (18.5%) patients experienced post-treatment ALT flares (median ALT 190 U/mL, range 110-1355 U/mL), resulting in ALT normalization and HDV-RNA negativity within 12-24 weeks. In all 5 patients, HDV-RNA had declined rapidly during LNF treatment, followed by gradual rises on-therapy to near BL levels, associated with decreased LNF exposure (due to dose reductions or excessive GI side effects). HBV DNA levels increased in all 5 patients by at least 3 logs (none had received concomitant nucleotide analog treatment). Post-flare HBV DNA levels were suppressed in all 5 patients (<1000 IU/mL) and undetectable in 2 patients. HBsAg in one patient decreased from 3900 IU/mL to <10 IU/mL. Two patients with intermittent low level HDV-RNA (BLOQ) post-ALT flare were retreated with 24 weeks low dose LNF (LNF 50 mg BID + RTV). HDV-RNA PCR-negativity was achieved soon after restarting treatment, and has remained so to date >12 weeks post-ending retreatment. Fibrosis grade decreased compared to BL from 4 to 3, 2 to 0 and 6 to 4, respectively, in the 3 patients rebiopsied 6-18 months following initial ALT normalization and HDV-RNA negativity.

Conclusions: LNF can induce therapeutic post-treatment immunological flares—a phenomenon heretofore not described in CDH. Thus, at least two pathways for achieving HDV negativity with LNF therapy exist: LNF-induced progressive suppression to HDV negativity on-treatment, and LNF-induced post-treatment anti-HDV therapeutic flares.

2. Background – Hepatitis Delta (HDV)

- HDV leads to the most severe form of viral hepatitis
  - More rapid progression to liver cirrhosis
  - More likely to develop HCC / decompensation vs HBV
- HDV is always associated with HBV Infection
  - HDV steals HBsAg from HBV for envelopment
- Prenylation is critical for HDV morphogenesis
  - HDV hijacks prenylation, a host process
- No FDA approved Rx for HDV
  - PEG IFN-α demonstrates modest benefit
- HDV worldwide prevalence is 15 - 20 million
  - Approximately 4-6% of HBV worldwide population is infected with HDV
  - Orphan status in US and EU





3. Background: Lonafarnib (LNF)

- Lonafarnib is a small molecule, oral, prenylation inhibitor
- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck
  - Dose limiting toxicity is GI (class effect)
- Prenylation is a host target; potential high barrier to resistance
- LOWR HDV (LOnafarnib With Ritonavir in HDV) Program
  - Identify dose and regimen for registration study
- Over 120 HDV patients dosed across 3 international sites

4. Background: LOWR HDV – 1 and LOWR HDV – 2* Study

Purpose:

To identify combination regimens of **LNF and RTV ± PEG IFN-α** which demonstrate efficacy and tolerability for longer term dosing to enable HDV-RNA clearance

Observations:

- LNF suppresses HDV-RNA < LOQ at end of treatment
- ALT normalizes in majority of patients at end of treatment
- Subset of patients who do not clear HDV-RNA on-treatment have become HDV-RNA negative post-treatment

5. Post-Treatment Analysis in LOWR HDV -1 and LOWR HDV - 2

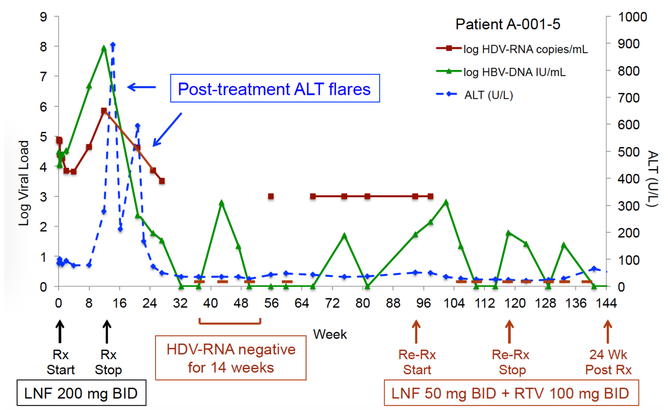
LOWR HDV – 1
"Combinations"
4 - 12 Weeks
N = 21

LOWR HDV – 2
"Dose-Finding"
12 - 48 Weeks
N = 58

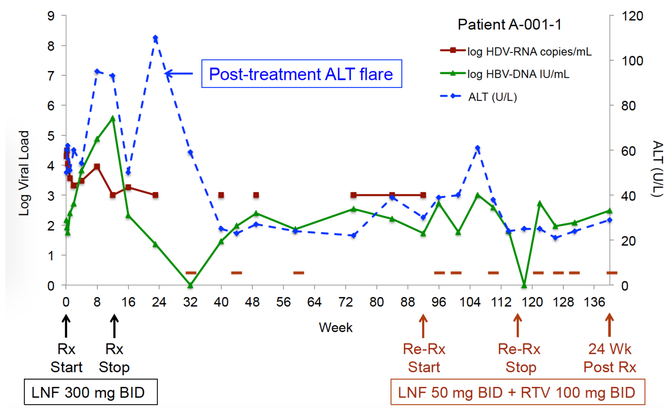
- 27 patients were analyzed who had detectable HDV-RNA after receiving LNF for 12 or 24 weeks in the LOWR HDV-1 and LOWR HDV-2 trials
- 5 patients identified with post-treatment ALT flares followed by HDV-RNA negativity
- 2 of 5 patients with HDV-RNA rebound were re-treated with low dose LNF
- Testing frequency: Q4W
  - Biochemical parameters and HBV DNA
  - HDV-RNA (by in-house qPCR with LOQ ~ 3 log copies/mL)

6. Results: Re-treatment with Low Dose LNF-regimen Drives HDV-RNA to PCR-negativity

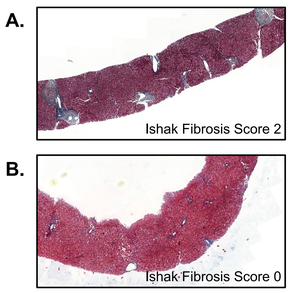
HDV-RNA Negative for 24 Weeks Post-Retreatment



HDV-RNA Negative for 24 Weeks Post-Retreatment



Patient A-001-1
2 Point Improvement in Fibrosis



A. Baseline

B. Week 128: 18 months post-ALT normalization and HDV-RNA negativity

7. Conclusions

Summary of Observations from Individual Cases:

- Post-treatment ALT flares observed in some LNF-treated HDV patients
- Post-treatment ALT flares are followed by:
  - Normalizing ALT levels
  - Sustained HDV-RNA negativity
    OR
  - HDV-RNA < LOQ, alternating with negativity
- Re-treatment with LNF 50 mg BID + RTV 100 mg BID for 6 months:
  - Rapid achievement of HDV-RNA negativity on re-treatment
  - HDV-RNA negativity sustained throughout re-treatment
  - HDV-RNA negativity sustained > 6 months post-treatment
- Long term ALT normalization has resulted in reversal of fibrosis

6. References

*Yurdaydin, C. et al; 2017 EASL Abstract #GS-008.

7. Disclosures

Lonafarnib was provided by Eiger Biopharmaceuticals, Inc. Glenn: Equity interest in Eiger Biopharmaceuticals, Inc. Yurdaydin: Received partial travel support from Eiger BioPharmaceuticals, Inc. to attend scientific meetings. All other authors have no financial disclosures.