Modeling Hepatitis Delta Virus (HDV) Dynamics During Ritonavir Boosted Lonafarnib Treatment—The LOWR HDV-3 Study

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*These authors contributed equally.
My presentation includes discussion of off-label/investigational use of lonafarnib and ritonavir

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HDV Infection: the least common form of viral hepatitis has the worst outcomes

- 15-20 million people are infected worldwide with HDV
- Up to 80% of patients with HDV may develop cirrhosis within 5-10 years
- Higher risk for hepatic decompensation leading to death & development of HCC compared to HBV mono-infected patients

The quest for better therapies against HDV

- Interferon-alpha therapy is unsatisfactory
  - <30% achieve HBsAg loss and become HDV RNA negative
  - Extended duration of therapy (>1 yr) does not improve HDV response rates

- Nucleos(t)ide analogues are ineffective

- Daily IV infusion (for 4 weeks) of silibinin is ineffective (case study)

- Investigational Therapies (in clinical trials)
  - Human sodium-taurocholate cotransporting polypeptide – Myrcludex B
  - Nucleic acid polymers – REP 2139
  - Prenylation inhibition – Lonafarnib
  - Peg-Interferon-lambda

References:
HDV life cycle and prenylation inhibitor Lonafarnib (LNF)

- HDV has a negative sense, circular RNA genome 1700 bases in length
- Encodes only one protein of its own, HDag, in two forms, large (LHDag) and small (SHDag)
- Uses hepatitis B surface antigen (HBsAg) to create its envelope and to achieve secretion

Prenylation (lipid modification) plays a vital part in the life cycle of HDV.

Lonafarnib (LNF) disrupts prenylation of the LHDag and prevents its ability to interact with HBsAg

The beginning of an era of HDV dynamics

- Understanding HDV dynamics is in its infancy due to limited studies with frequent kinetic data and the availability of only one medication (peg-IFN-α) with activity against HDV.

- In a previous study modeling HDV and HBsAg kinetics, we provided initial insights into HDV-HBsAg-host dynamics and IFN-α’s mode of action (MOA) and its efficacy against HDV.
Lonafarnib (LNF) phase 2 program provides important data (N>100) for viral kinetic analysis and mathematical modeling.

<table>
<thead>
<tr>
<th>Proof of Concept</th>
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<tbody>
<tr>
<td>• Monotherapy N = 14</td>
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<table>
<thead>
<tr>
<th>LOWR HDV – 1</th>
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<tbody>
<tr>
<td>• ± RTV or PEG IFN-α N = 21</td>
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<tr>
<th>LOWR HDV – 2</th>
</tr>
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<tbody>
<tr>
<td>• Dose Finding ± PEG IFN-α N = 58</td>
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<tr>
<th>LOWR HDV – 3</th>
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<tbody>
<tr>
<td>• QD Dose N = 21</td>
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<tr>
<th>LOWR HDV – 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose-Escalation N = 15</td>
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</table>

Modeling HDV kinetics during LNF-based therapy provides a novel opportunity to further characterize:

- HDV-host dynamics
- the antiviral effect of LNF and IFN-α and their MOA against HDV
- the dynamics between HDV and HBV replication


Koh et al., EASL 2017 Abstract #LBP-519
Wedemeyer et al., EASL 2017 Abstract #PS-039
Yurdaydin, C. et al, AASLD 2016 Abstract #1845
Modeling provides a strong rationale for ritonavir boosting of LNF

- PK/PD modeling predicts that a LNF monotherapy dose of 610 mg bid would achieve 99% efficacy, however, LNF maximum tolerated dose was 200 mg bid.

- LNF 100 mg bid with ritonavir (RTV) boosting exceeded the predicted 99% efficacy concentration and was associated with dramatic HDV viral load declines and better tolerability than higher doses of LNF monotherapy.
How can modeling be used to optimize therapy?

- Real-time modeling of viral kinetics can be used to individualize duration of therapy
- Modeling empowers a patient to participate in shared decision making regarding length of treatment

Dahari et al 2015; Liver International ; 35(2):289-294
LOWR-3 study design

- Phase 2a, Double Blinded, Randomized, Placebo-Controlled Study
- Lonafarnib (LNF) 50, 75 or 100 mg with ritonavir (RTV) 100 mg daily

Eligibility Screening

- LNF 50 mg + RTV 100 mg daily x 24 wk (n=4)
- LNF 75 mg + RTV 100 mg daily x 24 wk (n=4)
- LNF 100 mg + RTV 100 mg daily x 24 wk (n=4)

PBO x 12 wks -> LNF 50 mg + RTV 100 mg daily x 12 wk
PBO x 12 wks -> LNF 75 mg + RTV 100 mg daily x 12 wk
PBO x 12 wks -> LNF 100 mg + RTV 100 mg daily x 12 wk

Post-Therapy Follow-up x 24 wk

* All eligible subjects were placed/maintained on HBV nucleos(t)ide therapy for the duration of the study
Patient characteristics

* All subjects were placed/maintained on HBV nucleos(t)ide therapy for the duration of the study

* No difference in baseline parameters between placebo and treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (n=21)</th>
</tr>
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<tbody>
<tr>
<td>Male Sex (%)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>40 (32, 49)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.7 (22.5, 22.8)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Laboratory Results (IQR)</th>
</tr>
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<tbody>
<tr>
<td>ALT U/L</td>
</tr>
<tr>
<td>AST U/L</td>
</tr>
<tr>
<td>HBV DNA IU/mL</td>
</tr>
<tr>
<td>HDV RNA log IU/mL</td>
</tr>
<tr>
<td>Fibroscan kPa</td>
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</table>
Goals

- To characterize viral kinetics and provide insights into HDV-HBsAg-host dynamics during LNF+RTV treatment using mathematical modeling
- Analysis based on 12 patients dosed for 24 weeks with frequent sampling

Eligibility Screening

- PBO x 12 wks -> LNF 50 mg + RTV 100 mg daily x 12 wk
- PBO x 12 wks -> LNF 75 mg + RTV 100 mg daily x 12 wk
- PBO x 12 wks -> LNF 100 mg + RTV 100 mg daily x 12 wk

Post-Therapy Follow-up x 24 wk
Viral kinetic analysis identified 4 distinct patterns of response.
Four patterns of response seen in each LNF dosing group

**Triphasic Response**
LNF 50 mg QD / RTV 100 mg QD

**Flat Partial Response**
LNF 50 mg QD / RTV 100 mg QD

**Rebound**
LNF 50 mg QD / RTV 100 mg QD

**Non-Response**
LNF 50 mg QD / RTV 100 mg QD
HBsAg and ALT kinetic characterization

- HBsAg levels did not change on therapy

- ALT Normalization
  - 100% of triphasic responders
  - 67% of flat partial responders
  - ALT levels fluctuated in rebounders
LNF and RTV kinetics

- There was no association between LNF conc. and viral response patterns.
- Peak RTV levels > 1200 ng/ml were associated with a triphasic response.
HDV rebound associated with decline in LNF conc.

There is no evidence of virological resistance
Modeling HDV RNA, HBsAg and ALT kinetics

- (T) is the number of HBsAg-productive cells that could be infected with HDV (V) to become (I)

- T+I can proliferate with maximum proliferation rate r, according to a blind homeostasis process.

- Pre-treatment steady state was assumed

- LNF efficacy (%) in blocking HDV production is represented by ε
Triphasic cases – model fits well

Modeling curves: HDV RNA (solid line), HBsAg (dashed line) and ALT (dotted line)
Flat partial response – model fits well

Modeling curves: HDV RNA (solid line), HBsAg (dashed line) and ALT (dotted line)
Rebounders – model fits well

Modeling curves: HDV RNA (solid line), HBsAg (dashed line) and ALT (dotted line)
Triphasic response is explained by drug efficacy ($\varepsilon$) higher than patient’s critical drug efficacy ($\varepsilon_c$).

<table>
<thead>
<tr>
<th>Pt</th>
<th>Viral kinetic pattern (LNF dose)</th>
<th>Estimated LFN +RTV efficacy in blocking HDV production ($\varepsilon$)</th>
<th>Estimated critical drug efficacy in each patient ($\varepsilon_c$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Triphasic (50)</td>
<td>0.70</td>
<td>0.50</td>
</tr>
<tr>
<td>2</td>
<td>Triphasic (75)</td>
<td>0.93</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>Triphasic (100)</td>
<td>0.68</td>
<td>0.42</td>
</tr>
<tr>
<td>4</td>
<td>Flat partial (50)</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>5</td>
<td>Flat partial (75)</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>6</td>
<td>Flat partial (100)</td>
<td>0.70</td>
<td>0.77</td>
</tr>
<tr>
<td>7</td>
<td>Rebound (50)</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>8</td>
<td>Rebound (75)</td>
<td>0.96</td>
<td>0.97</td>
</tr>
<tr>
<td>9</td>
<td>Rebound (100)</td>
<td>0.85</td>
<td>0.66</td>
</tr>
</tbody>
</table>

When $\varepsilon > \varepsilon_c$ viral load is predicted to decline in a triphasic manner.

When $\varepsilon < \varepsilon_c$ viral load is predicted to decline in a flat partial response manner.

estimated $\varepsilon$ before viral rebound
Predicting time to < 1 HDV particle in the entire extracellular-body fluid

**Patient 1**
- LNF/RTV 50/100 mg
- Assay limit (14 IU/ml)
- Projected time to HDV RNA < 1 particle after 49 wk of LNF/RTV
- <1 HDV RNA in extracellular fluid

**Patient 3**
- LNF/RTV 100/100 mg
- Assay limit (14 IU/ml)
- Projected time to HDV RNA < 1 particle after 51 wk of LNF/RTV
- <1 HDV RNA in extracellular fluid
Summary

- LNF+RTV was safe and generally well tolerated

- The kinetic analysis indicates that there is no association between ritonavir boosted lonafarnib dosing (50, 75 or 100 mg daily) and viral response pattern (i.e., triphasic response, flat-partial response and rebound)

- The model was able to reproduce the observed viral, HBsAg and ALT kinetics in each patient and provided insights into viral-host-drug dynamics

- Modeling results show high antiviral efficacy (95%) with ritonavir boosted lonafarnib
The results suggest that on treatment (real time) modeling may help individualize the length of lonafarnib-based therapy that is needed to achieve HDV clearance.
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Scott J Cotler

Cihan Yurdaydin

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Adverse Events

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group Significance</th>
<th>Score Difference (100 pt scale)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>50 vs 100 mg LNF</td>
<td>8.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal Bloating</td>
<td>75 vs 100 mg LNF</td>
<td>10.7</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

No significant changes in weight in all subjects
No Grade 3 or 4 adverse events
No discontinuations due to adverse events