Prenylation Inhibition with Lonafarnib Decreases Hepatitis D Levels in Humans

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Introduction

• 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 mono-infected patients

The Quest For Better Therapies

• Interferon therapy is unsatisfactory
  – <30% achieve HBsAg loss and become HDV RNA negative
  – Extended duration of therapy does not help

• Nucleos/tide analogues are ineffective

• Investigational Therapies
  – HBV/HDV NTCP receptor entry inhibitor
  – HDV prenylation inhibitor

Lau DT, et al. Gastroenterol 1999;117
Prenylation Inhibition in HDV

- Prenylation inhibitors have demonstrated effectiveness against HDV in *in vitro* and *in vivo* models.

Bordier et al. J Clin Invest 2003;112
Einav S, Glenn JS. J Antimicrob Chemother 2003; 52
NIH HDV Lonafarnib Study

• Phase 2A, Double Blinded, Randomized, Placebo Controlled Study

• Endpoints:
  – Therapeutic: Improvement in quantitative HDV RNA levels after 28 days of lonafarnib therapy
  – Safety: Ability to tolerate lonafarnib at the prescribed dose for 28 days.
NIH HDV Lonafarnib Study Design

Group 1: Lonafarnib 100 mg BID, 6 Treatment : 2 Placebo

- 3 Eligibility Evaluations
- 28 days of Therapy
- 6 Months Follow-up

Group 2: Lonafarnib 200 mg BID, 6 Treatment : 2 Placebo

- *
- 3 Eligibility Evaluations
- 28 days of Therapy
- 6 Months Follow-up

*Group 1 Placebo patients offered open-label Lonafarnib 200 mg
22 Patients with +HDVAb Screened

14 Patients with +HDV RNA Enrolled

8 Patients Not Enrolled
8 Patients Not Enrolled
4 HDV RNA Undetectable
3 Did Not Complete PreTx Evaluation
1 with Hepatocellular Carcinoma

8 Patients Lonafarnib 100mg BID

6 Blinded Treatment
2 Blinded Placebo

8 Patients Lonafarnib 200 mg BID

2 Open-Label Treatment
2 Blinded Placebo
4 Blinded Treatment
# Patient Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>71%</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>38 (29-61)</td>
</tr>
<tr>
<td>Nucleoside Analogue</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Race**

<table>
<thead>
<tr>
<th>Race</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>43%</td>
</tr>
<tr>
<td>Asian</td>
<td>50%</td>
</tr>
<tr>
<td>African</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Median Laboratory Results (IU/mL)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>89</td>
</tr>
<tr>
<td>AST</td>
<td>61</td>
</tr>
<tr>
<td>HDV RNA</td>
<td>1.01E+06</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&lt;21</td>
</tr>
</tbody>
</table>

**Median Histology**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishak Fibrosis</td>
<td>3</td>
</tr>
</tbody>
</table>

*No difference in baseline parameters between placebo and treatment groups*
HDV Decline During Therapy

Median HDV Decline From Baseline (log IU/mL)

- Placebo
- 100mg BID
- 200mg BID

Day of Therapy

0 7 14 21 28

-2.0
-1.5
-1.0
-0.5
0.0
0.5

National Institute of Diabetes and Digestive and Kidney Diseases
HDV RNA Decline After 28 Days of Therapy

- Placebo: -0.13
- 100mg BID: -0.73
- 200mg BID: -1.54

p=0.002, p=0.04, p=0.01
Correlation of Serum Drug Concentration and Change in HDV RNA

Mean Serum Lonafarnib Concentration (ng/mL)

Mean Change HDV RNA From Baseline to Day 28 (log IU/mL)

$r^2 = 0.78$
HDV Resistance Testing

• Population-Based Sequencing of LDAg (codons 115-215) from Serum
  – Baseline
  – End of Therapy (Day 28)
  – End of Study (24 weeks post-therapy)

• Lonafarnib 100 mg BID
  – Completed

• Lonafarnib 200 mg BID
  – Baseline and End of Therapy (Day 28): Completed
  – End of Study (24 weeks post-therapy): Pending

⇒ NO RESISTANCE SEEN
## Symptoms & Side Effects

### Lonafarnib 100 mg BID

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Loose Stools</td>
<td>3</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Bloating</td>
<td>1</td>
</tr>
</tbody>
</table>

### Lonafarnib 200 mg BID

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
</tbody>
</table>

**Weight Loss (mean)**

| Weight Loss (mean) | 6 (4 kg) |

No Subject Experienced a Grade 3 or 4 Adverse Event
No Subject Experienced a Serious Adverse Event
Summary

• After 28 days of therapy with lonafarnib, serum HDV RNA was significantly lower in both treatment groups compared to placebo
• A dose dependent reduction in serum HDV RNA was seen with lonafarnib therapy
• Serum lonafarnib concentrations correlate with HDV RNA decline
Summary

- No HDV resistance was identified during population-based sequencing of LDAg
- Lonafarnib was generally well tolerated at the prescribed doses for 28 days
Conclusion

• This is the first demonstration that treatment of chronic HDV with the prenylation inhibitor lonafarnib significantly reduces virus levels in patients.

• The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV.
Future Directions

• Single and Multi-National confirmation studies evaluating
  – Dosing
  – Duration
  – Efficacy
Acknowledgements

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Mark A Winters

Harel Dahari
Laetitia Canini