Session
Viral Hepatitis B & D: Clinical
Saturday April 25, 2015
Cihan Yurdaydin, MD
Optimizing the prenylation inhibitor lonafarnib using ritonavir boosting in patients with chronic delta hepatitis

Cihan Yurdaydin, Ramazan Idilman, Ingrid Choong, Cagdas Kalkan, Onur Keskin, M Fatih Karakaya, E Ali Tuzun, Ersin Karatayli, Mithat Bozdayi, David Cory, Jeffrey S Glenn
Hepatitis D Virus

- HDV is always associated with HBV Infection
- HDV worldwide prevalence is 15 million
- HDV is the most severe form of viral hepatitis
  - More rapid progression to liver cirrhosis and liver cancer
- No FDA approved Rx for HDV
  - In absence of an approved therapy, HDV screening is limited
Classic Antivirals Ineffective Against HDV

- IFN-α effective in ~ 25% of chronic HDV patients
- HBV nucleos(t)ide analogs (NAs) are ineffective
- IFN-α + NAs (HIDIT 1 / HIDIT 2) no better than IFN
- No direct acting agents have been studied for HDV
Prenylation is Key to HDV Life Cycle

Farnesyl Transferase Inhibitors Target Prenylation

- Entry Inhibitors
- Attachment
- Blocked by prenylation inhibitors

- Hepatocyte
- HBsAg
- Transfer
- Replication
- Virion assembly
- Export


e.g. Farnesyl transferase inhibitors

HDV
HBsAg
Prenylation Inhibitors as Antivirals
Compelling Preclinical Rationale

Identification of a Prenylation Site in Delta Virus Large Antigen
Jeffrey S. Glenn,* John A. Watson, Christopher M. Havel, Judith M. White
SCIENCE • VOL. 256 • 29 MAY 1992

Use of a Prenylation Inhibitor as a Novel Antiviral Agent
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A Prenylation Inhibitor Prevents Production of Infectious Hepatitis Delta Virus Particles
Bruno B. Bordier,1,2 Patricia L. Marion,1 Kazuo Ohashi,3 Mark A. Kay,3 Harry B. Greenberg,1,2,4†
John L. Casey,5 and Jeffrey S. Glenn1,2,6,7
Division of Gastroenterology and Hepatology,1 Department of Microbiology and Immunology,4 and Program in Human
Gene Therapy, Departments of Pediatrics and Genetics,1 Stanford University School of Medicine, and Veterans
Administration Medical Center,2 Palo Alto, California, and Division of Molecular Virology and Immunology, Georgetown University Medical Center, Rockville, Maryland5

In vivo antiviral efficacy of prenylation inhibitors against hepatitis delta virus
The Journal of Clinical Investigation | August 2003 | Volume 112 | Number 3 | Jeffrey S. Glenn
Lonafarnib
Well-Characterized Clinical Stage Lead Compound

- Small molecule, oral, inhibitor of farnesyl transferase

- Inhibits farnesylation of large delta antigen
  - Blocks assembly and packing of viral particles
  - High theoretical barrier to resistance

- Phase 2a POC in HDV infected patients completed
  - NIH study presented at 2014 AASLD (Boston)
PEG IFN-α 2a* versus Lonafarnib in HDV

% Patients Achieving ≥ 1 Log Decline in HDV-RNA

PEG IFN-α 2a* versus Lonafarnib in HDV

% Patients Achieving ≥ 1 Log Decline in HDV-RNA

HIDIT - 2

PEG IFN α 2a
180 mcg QW
+ Tenofovir QD

NIH
LNF
100 mg
BID

NIH
LNF
200 mg
BID

PEG IFN-α 2a* versus Lonafarnib in HDV

% Patients Achieving ≥ 1 Log Decline in HDV-RNA

HIDIT - 2

PEG IFN α 2a 180 mcg QW + Tenofovir QD

NIH

LNF 100 mg BID

LNF 200 mg BID

% Patients Achieving ≥ 1 Log VL Decline

Week 4  Week 12  Week 48

33%  68%  79%

NIH

100%

Aims of Study

Explore if efficacy can be optimized by:

• increasing lonafarnib dose
• increasing lonafarnib intake frequency
• combination therapy with peg-interferon
• combination therapy with ritonavir
Patients and Methods

• Treatment duration 4 - 8 weeks

• 72 hour PK and PD evaluation on day 1 and day 28

• Testing frequency: days 1, 2, 3, 7, 14, 28 and then Q2W
  – Biochemical parameters
  – HDV RNA (by in-house quantitative real-time PCR)
  – HBV DNA (by Cobas, Taqman, Amplicor)
LOWR HDV – 1 Study
LOnafarnib With and without Ritonavir in HDV

- n=3
  - Lonafarnib 200 mg BID
- n=3
  - Lonafarnib 300 mg BID
- n=3
  - Lonafarnib 100 mg TID
- n=3
  - Lonafarnib 100 mg BID + Ritonavir 100 mg QD
- n=3
  - Lonafarnib 100 mg BID + PEG IFN-α 180 mcg QW

Assess: Efficacy, Tolerability, PK, Viral Load

Month 1
Day 28 Reduction in Serum HDV RNA

- Lonafarnib 100 mg BID
- Lonafarnib 100 mg BID + Ritonavir 100 mg QD + PEG IFN α 2a 180 mcg QW

Change in Log HDV RNA copies/mL:
- Lonafarnib 100 mg TID
  - Mean ∆ - 1.5 Log
  - N = 3

- Lonafarnib 200 mg BID
  - Mean ∆ - 1.6 Log
  - N = 3

- Lonafarnib 300 mg BID
  - Mean ∆ - 2.0 Log
  - N = 3

- Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW
  - Mean ∆ - 2.2 Log
  - N = 3

Mean ∆ - 1.8 Log
N = 3
Day 28 Reduction in Serum HDV RNA

NIH (AASLD 2014)

Lonafarnib 100 mg BID
Lonafarnib 200 mg BID
Placebo

Mean ∆ - 0.2 Log
Mean ∆ - 0.74 Log
Mean ∆ - 1.6 Log
Mean ∆ - 1.5 Log
Mean ∆ - 1.6 Log

LOWR-1

Lonafarnib 100 mg BID + Ritonavir 100 mg QD
Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW

Lonafarnib 300 mg BID
Lonafarnib 200 mg BID + PEG IFN α 2a 180 mcg QW

Lonafarnib 200 mg BID
Lonafarnib 300 mg BID

Mean ∆ - 2.0 Log
Mean ∆ - 2.2 Log
Mean ∆ - 1.8 Log

N = 4
N = 6
N = 6
N = 3
N = 3
N = 3
N = 3
N = 3
Day 28 Reduction in Serum HDV RNA

NIH (AASLD 2014)

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<th>Treatment</th>
<th>N</th>
<th>Mean ∆ Log</th>
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<tr>
<td>Placebo</td>
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<td>Lonafarnib 100 mg BID</td>
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<tr>
<td>Lonafarnib 200 mg BID</td>
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LOWR-1

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<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean ∆ Log</th>
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<tr>
<td>Lonafarnib 100 mg BID</td>
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<td>-1.8</td>
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<tr>
<td>Lonafarnib 200 mg BID + Ritonavir 100 mg QD</td>
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<td>-2.0</td>
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<tr>
<td>Lonafarnib 300 mg BID</td>
<td>3</td>
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<tr>
<td>Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW</td>
<td>3</td>
<td>-2.2</td>
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</table>
**LOWR HDV – 1**

**LOnafarnib With and without Ritonavir**

**Month 1**

**Boost with Ritonavir**

- N=3
- Lonafarnib 100 mg BID + Ritonavir 100 mg QD

**Complement with PEG IFN**

- N=3
- Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW

**Month 2**

- Lonafarnib 100 mg BID + Ritonavir 100 mg QD
- Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW

**Assessments:** Safety, Tolerability, HDV-RNA, PK
Viral Load Declines on Lonafarnib + Ritonavir

Week 4 Mean Change in HDV-RNA Viral Load: -2.2 Log
Week 8 Mean Change in HDV-RNA Viral Load: -3.2 Log

Lonafarnib 100 mg BID + Ritonavir 100 mg QD

Post-treatment

BLQ = below limit of quantification
Normalization of ALT on Lonafarnib + Ritonavir

ALT Levels Maintained After Treatment

Lonafarnib 100 mg BID + Ritonavir 100 mg QD

Post-treatment

ALT Levels:
- Normal 10-40 U/L

Week

0  2  4  6  8  10  12

Patient 1
Patient 2
Patient 3

PaBent 1
PaBent 2
PaBent 3
Lonafarnib PK Boosted by Ritonavir
Serum Concentration Increased 4-5 Fold

Graph showing the mean serum lonafarnib concentration (ng/ml ± SD) over days of treatment for two groups: 100 mg lonafarnib BID [n = 6] and 100 mg lonafarnib BID + 100 mg RTV QD [n = 3].
Viral Load Declines on Lonafarnib + Peg IFN

Week 4 Mean Change -1.8 Log
Week 8 Mean Change -3.0 Log

LNF 100 mg BID + PEG IFN 180 mcg QW

Post-treatment

Change in Log HDV RNA copies/mL

Week
ALT Improvement of Lonafarnib + PEG IFN

ALT Levels Continue to Decline After Treatment

Lonafarnib 100 mg BID + PEG IFN α 2a 180 mcg QW

Post Treatment

Week 0

Week 12

0

10-40 U/L

Normal

Week 0

Week 4

Week 5

Week 8
Earlier VL Decline with Lonafarnib Combination

Lonafarnib Combinations Display Biphasic Kinetics and More Rapid Onset

Mean Viral Load Change (Log Copies/mL)

Week

On-Treatment

Post-treatment

LNF 100 mg BID + RTN 100 mg QD (N=3)

LNF 100 mg BID + PEG IFN-α 2a 180 mcg QW (N=3)
Earlier VL Decline with Lonafarnib Combination

Lonafarnib Combinations Display Biphasic Kinetics and More Rapid Onset

Mean Viral Load Change (Log Copies/mL) vs Week

On-Treatment vs Post-treatment

HIDIT-2: PEG IFN 180 mcg QW ± tenofovir QD (N=91)

LNF 100 mg BID + RTN 100 mg QD (N=3)

LNF 100 mg BID + PEG IFN-α 2a 180 mcg QW (N=3)
Earlier VL Decline with Lonafarnib Combination

Lonafarnib Combinations Display Biphasic Kinetics and More Rapid Onset

Mean VL Change (Log IU/mL)

Week

LNF 100 mg BID + PEG IFN 180 mcg QW (N=3)

LNF 100 mg BID + RTN 100 mg QD (N=3)

HIDIT-2: PEG IFN 180 mcg QW ± tenofovir QD (N=91)
Side effects Improved with LNF Combos

- Mainly GI side effects

<table>
<thead>
<tr>
<th>Grade</th>
<th>N=3 LNF 200 mg BID</th>
<th>N=3 LNF 300 mg BID</th>
<th>N=3 LNF 100 mg BID RTN 100 mg QD</th>
<th>N=3 LNF 100 mg BID PEG IFN 180 mcg QW</th>
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<tr>
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<td>Anorexia</td>
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</tbody>
</table>

- Graded according to **Common Terminology Criteria for Adverse Events**
- Lonafarnib chronically dosed in Progeria for 2 years (PNAS, 2012, 16666)
Summary and Conclusions

- LOWR – 1 Study: promising combos for further exploration
  - Lonafarnib + Ritonavir ≥ 3 log drop at Month 2
  - Lonafarnib + Pegasys ≥ 3 log drop at Month 2

- LOWR – 2 Study: “Dose-Finding” study on-going
  - Exploring lonafarnib + ritonavir combinations for longer dosing

- Lonafarnib is first oral therapy for HDV
  - More rapid onset than PEG-IFN
  - Host-targeting Rx with high barrier to resistance