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Chronic Liver Disease Foundation

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Hepatitis Delta Virus (HDV)

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Overview of HDV

- HDV Virology
- HDV Epidemiology and Disease Burden
- Management of HDV
- New HDV treatments in Development
  - Bulevirtide
  - Rep 2139
  - Lonafarnib
  - Peginterferon Lambda
Hepatitis Delta Virus (HDV)

Overview

- HDV is the most severe form of human viral hepatitis
- HDV is a coinfection with HBV
  - HBsAg is acquired by HDV through protein prenylation
- In the US, at least 4 – 6% of HBV infected patients are coinfectected with HDV
- HDV/HBV coinfection causes more rapid disease progression as compared to HBV monoinfection
- Currently, there are no FDA approved treatments for HDV
- 15 – 20M HDV infected persons worldwide
  - > 100K in US
  - > 200K in EU
  - > 2M in China

HDV consists of a single stranded, circular RNA genome, with an envelope made up of HBsAg.

- HDV requires HBsAg to complete virus assembly
- Assembly with HBsAg is mediated by large delta antigen prenylation

HDV Life Cycle

Attachment and entry

Transport to Nucleus

Replication

Assembly

Release of Progeny

HDV genome encodes for a single protein, the hepatitis delta antigen.

HDV relies on host cell machinery for replication.

New virions can be assembled only in the presence of hepatitis B virus.

<table>
<thead>
<tr>
<th>HDV genome</th>
<th>small HDAg</th>
<th>large HDAg</th>
<th>prenylated LHDAg</th>
<th>prenyl moiety</th>
<th>HBsAg</th>
</tr>
</thead>
</table>
HDV Worldwide Prevalence: 15 – 20 Million

6% of HBV Population Coinfected with HDV
HDV Geographic Footprint Is Growing

U.S. Major Metro Hotspots Identified

Top 10 U.S. Cities in 2016

1. Chicago, Illinois
2. Berwyn, Illinois
3. Brooklyn, New York
4. Corona, New York
5. Waukegan, Illinois
6. New York, New York
7. Bronx, New York
8. Jamaica, New York
9. Lombard, New York
10. Aurora, Illinois

U.S. HDV Prevalence In 2018 ~110,000

Increased Screening Leads to Increased HBV and HDV Diagnosis

* 11.8% of HBV Patients Co-infected with HDV

Newly Diagnosed HDV Patients in the U.S. Each Year*

HDV: Most Rapid Progression of Viral Hepatitis

Progression to Cirrhosis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>10 – 20% within 20 Years</td>
</tr>
<tr>
<td>HBV</td>
<td>20% within 5 Years</td>
</tr>
<tr>
<td>HDV</td>
<td>70% within 5 – 10 Years</td>
</tr>
</tbody>
</table>

HDV Causes Most Rapid Disease Progression

At Diagnosis, > 50% of HDV Patients Are Cirrhotic

Survival: HDV vs Cancer

HDV Clinical Course and Outcomes

HDV: A Devastating Disease with No Approved Treatment

- **High Disease Burden**: ~70% Cirrhotic within 5-10 years
- **Low Survival Rate**: ~60% Mortality within 10 years
- **High Cost Transplants**: ~$575K Cost and >14,000 Waiting List

25% of People on Waiting List Die Each Year Before Receiving a Liver Transplant

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Current Management

- No FDA-approved therapy for HDV
- IFN alpha (+/- PEG) is only drug with any demonstrated efficacy
- Suboptimal due to:
  - Significant side effects (including cytopenias)
  - Limited efficacy
  - High long-term relapse rates
Current Management

- ~2.5 log decline in median HDV RNA at EOT
- 25% neg 24 wks post Rx in patients receiving PEG-IFN
- 0% with nucleoside analog alone (no effect on HBsAg)

HBV Therapies Do Not Eradicate HDV

HBV Functional Cures Will Not Eradicate HDV

• Approved HBV nucleos(t)ide treatments only suppress HBV DNA
  – They do not effect HBsAg and have no effect on HDV

• Investigational HBV treatments target functional cure
  – Not expected to completely eliminate HBsAg needed by HDV
Quest Diagnostics Launches Commercial HDV RNA Test

HDV RNA Quantification Is the Gold Standard in HDV Diagnosis and Management

• A leading provider of diagnostic services
• Over 2,200 patient service centers across the US
• Highly targeted patient and physician outreach
• HDV testing program for HBV-positive patients
• HDV RNA quantification and HBV/HDV reflex testing
HDV Treatments in Development

Entry Inhibitors (bulevirtide)

Attachment and entry

Transport to Nucleus

Replication

Nucleic Acid Polymers (REP 2139)

Release of Progeny

Assembly

Prenylation LHDAg

Preynlation Inhibitors (lonafarnib)

Peginterferon Lambda

HDV genome

small HDAg

large HDAg

prenylated LHDAg

prenyl moiety

HBsAg

LHDAg

large delta antigen

Small delta antigen

HBV surface antigen

Prenylation

Inhibitors

(bulevirtide)

Peginterferon Lambda

Entry Inhibitors (lonafarnib)

Interferon

Receptor

Jak

Stat

ISG

Induction

Antiviral Activity

HDV Treatments in Development
# HDV Treatments in Development

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Company</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonafarnib</td>
<td>EIGER</td>
<td>Daily Oral</td>
</tr>
<tr>
<td>Peginterferon Lambda</td>
<td>EIGER</td>
<td>Weekly SQ injection</td>
</tr>
<tr>
<td>Bulevirtide</td>
<td>MYR</td>
<td>Daily SQ injection</td>
</tr>
<tr>
<td>Rep-2139</td>
<td>replicor</td>
<td>Weekly IV infusion</td>
</tr>
</tbody>
</table>
Bulevirtide

Entry Inhibitor Targeting NTCP

- Daily, subcutaneous injections
- Synthetic 47 amino acid, N-acylated preS1 lipopeptide
- Targets Na-taurocholate cotransporting polypeptide (NTCP)
  - On surface of hepatocytes
- Blocks receptor functions of NTCP and HBV/HDV virus entry
Primary Endpoint
- HDV RNA < LLOD at 24 weeks post-tx (Week 72)

Secondary Endpoint
- HDV RNA < LLOD at Week 48
  - ALT nl at Week 48, 72
  - HDV RNA > 2 log decline and ALT nl at Week 48, 72
  - HBsAg undetectable or > 1 log decline at Week 48, 72
Phase 3 MYR301 Study

Across 7 Sites in Russia

Comparison for primary endpoint

Arm A (n=50)
- Week 0: NA
- Week 48: 10mg MyrB + NA
- Follow up (NA)

Arm B (n=50)
- Week 0: 10mg MyrB + NA
- Week 48: follow up (NA)

Arm C (n=50)
- Week 0: 2mg MyrB + NA
- Week 48: follow up (NA)

Composite primary endpoint:
HDV RNA negativation or >2log decline as well as ALT normalization
REP 2139

- Nucleic acid polymers (NAPs) are oligonucleotides with broad spectrum in vitro antiviral activities
- Reported to act via entry inhibition in other viruses
- Also proposed to bind to amphipathic protein structures
- These amphipathic protein structures are common in viral proteins, but are also found in key host cell proteins
- REP 2139 inhibits secretion of HBsAg from cells
Phase 2 REP 301 Study

- 12 HDV pts in Moldova
- Anti-HDV/RNA +
- HBsAg > 1000
- Non-cirrhotic

Responses mostly maintained on interferon
5 patients rebound with cessation of IFN (EASL 2017)
Responses maintained to date (EASL 2018)

Lonafarnib

First and Only Oral Therapy in Development for HDV

• Small molecule, first-in-class, oral prenylation inhibitor
• Well-characterized through Phase 3
  – > 2,000 subjects dosed in oncology program by Merck (Schering)
    – Dose limiting toxicity is GI (class effect)
• Over 120 HDV patients dosed across international sites
• US & EU Orphan Designation, FDA Breakthrough and EMA PRIME Designation
• Broad range of lonafarnib + ritonavir doses and durations studied
• US and multiple international sites
LOWR: Phase 2 Lonafarnib Study

Compared to PEG-IFN-alfa-2a Alone

All patients will be run-in and maintained on background HBV nucleoside therapy. Superiority over PEG IFN-alfa-2a not required.

* biopsy
Peginterferon Lambda

A Better Tolerated Interferon

• A novel, first-in-class Type III interferon
• Binds to a unique receptor versus Type I interferons
  – Highly expressed on hepatocytes
  – Limited expression on hematopoietic cells and CNS cells
• Uses similar downstream signaling pathway as Type I interferons
• Studied in > 3,000 subjects across 17 clinical trials (HCV / HBV)
• Comparable antiviral activity with less of the typical IFN alfa related side effects

LIMT: Phase 2 Lambda Study

A Better Tolerated Interferon for HDV Monotherapy

On-treatment
48 weeks

Mono
Lambda 120 mcg QW

Mono
Lambda 180 mcg QW

Post-treatment
24 weeks

Follow-up

Follow-up

Primary Endpoint:
• Evaluate Safety, Tolerability, Efficacy

Secondary Endpoint:
• Proportion of Patients with HDV RNA BLQ 24 weeks after EOT
Peginterferon Lambda Activity Through Week 48

Lambda 180 mcg has Comparable Antiviral Activity to Alfa 180 mcg with Improved Tolerability

Log HDV RNA IU/mL

Week

180 mcg
120 mcg

Peginterferon Lambda: 36% Durable Virologic Response

DVR Endpoint = BLQ at 24 Weeks Post-Treatment

Week 48
End of Treatment

Week 72
End of Follow-up

% Patients

BLQ

2/14
14%

ALT Normalization

5/14
36%

Etzion et al, EASL 2019, LIMT Phase 2 Study; Robogene® 2.0 HDV RNA PCR assay, LLOQ = 14 IU/mL; DVR = BLQ at 24 Weeks Post-Treatment
Lift: Phase 2 Lambda & Lonafarnib Combination Study

A Better Tolerated Interferon for Combination

**Primary Endpoint:**
- ≥ 2 Log HDV RNA reduction at EOT

**Secondary Endpoint:**
- Histological Improvement (biopsy confirmed)

- Median Decline of HDV RNA: -3.4 Log at Week 24
- 95% of Patients Achieve > 2 Log Decline in HDV RNA at Week 24
- > 50% of Patients Achieve Undetectable or BLOQ HDV RNA at Week 24

**N=26**
- Lambda 180 mcg QW
- Lonafarnib 50 mg BID
- Ritonavir 100 mg BID

**On-treatment**

**Post-treatment**

Follow Up

- Dosing
- End of Treatment Data Q4’19

* biopsy

**24 Weeks**
First-in-Class Treatments in Development for HDV

Multiple Options to Treat HDV

- Lonafarnib
  - Daily Oral Therapy
  - Combination Therapy
  - Weekly SQ Monotherapy

- PEG IFN Lambda
  - Monotherapy
  - Lonafarnib / Ritonavir + PEG IFN Lambda
Conclusions

- HDV is the most severe form of viral hepatitis
- HDV / HBV coinfection causes more rapid disease progression as compared to HBV monoinfection
- Understanding HDV life cycle has elucidated many potential host targets for antiviral intervention, including
  - Entry, prenylation, HBsAg secretion, IFN lambda signaling
- Several HDV therapies are now in Phase 2 and Phase 3 development
- Different therapeutic targets have potential for combination HDV antiviral therapy