HEPATITIS DELTA VIRUS (HDV)

OVERVIEW

- Most severe form of viral hepatitis
- Always associated with HBV infection
- HDV causes more rapid disease progression
  - Compared to HBV mono-infection
- No FDA approved Rx
  - PEG IFN alpha demonstrates modest benefit

Prevalence

- 15-20 M HDV infected patients worldwide
- 4-6% of HBV infected patients

Increased HDV Patient Diagnosis

~110,000 Individuals Co-infected with HBV/HDV in U.S.

Newly Diagnosed Patients by ICD-10

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
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<tr>
<td>2008</td>
<td>4,946</td>
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<td>2009</td>
<td>4,274</td>
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<tr>
<td>2010</td>
<td>4,841</td>
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<td>2011</td>
<td>5,043</td>
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<td>5,259</td>
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<tr>
<td>2013</td>
<td>5,926</td>
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<tr>
<td>2014</td>
<td>6,836</td>
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<tr>
<td>2015</td>
<td>7,442</td>
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<td>2016</td>
<td>9,079</td>
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Lonafarnib Phase 2 Data Presentations

Poster, DDW 2017, Abstract #Sa1486
**HDV WORLDWIDE PREVALENCE: 15-20 MILLION**

6% of HBV Population Infected with HDV
MIGRATION AND VIRAL HEPATITIS

Globalization of Disease

Foreign-born individuals comprise majority of growing HDV positive population in North America and Western Europe…

Germany: Wedemeyer et al., Hepatology 2007
France: Le Gal et al., Hepatology 2007
Italy: Stroffolini et al., J Med Virol 2009
Piccolo et al., Eur J Publ Health 2010
MIGRATION INTO WESTERN EUROPE

Known Claims for Asylum in 2015 > 1 Million

Source: Eurostat
AT DIAGNOSIS, >50% OF HDV PATIENTS ARE CIRRHOTIC

Risk of Hepatocellular Carcinoma, Decompensation, Mortality Increase

**PEG IFN-α HAS MODEST BENEFIT IN HDV**

Tolerability a Problem, Rebound a Problem, Retreatment a Problem

-2.5 log mean reduction in HDV-RNA at 48 weeks

SVR rates ~ 25-30%

Wobse 2014: AASLD
Wedemeyer 2014: AASLD
**REDUCING HDV-RNA IMPROVES SURVIVAL**

Improved Clinical Benefit without Clearance of HDV-RNA

Interferon-\(\alpha\) for 48 weeks with 15 year Follow Up

- **Change in HDV-RNA**
  - Log Change in Serum HDV-RNA
  - \(n=36\)
  - \(P = 0.009\)

- **Survival**
  - Proportion of Patients Surviving
  - Years after Termination of Therapy

Farci et al, Gastroenterology 2004: Long-Term Benefit of Interferon-\(\alpha\) Therapy of Chronic HDV: Regression of Advanced Hepatic Fibrosis
FEWER CLINICAL EVENTS FOLLOWING IFN α

HDV-RNA Loss Improves Long-term Clinical Outcomes

• Long term clinical outcomes
  - IFN alfa treatment in HDV

• Retrospective analysis
  - single cohort study

• 136 anti-HDV positive patients

• Median follow-up: 5.2 years
  - Range 0.6 - 18.8 years

Wranke et al. J Hepatology 2016: Does Antiviral Treatment Affect the Clinical Long-term Outcome of Hepatitis Delta?
WHAT ENDPOINTS HAVE BEEN USED IN HDV?
PROPOSED ENDPOINTS IN HDV

- Primary Endpoint: Reduction in HDV RNA
  - ≥ 2 Log Reduction in HDV RNA at EOT

- Secondary Endpoint: Biopsy Confirmed Histologic Improvement
  - 2 point improvement in HAI inflammation score without progression in Fibrosis at EOT
  - ALT Normalization at EOT

White Paper to be submitted by Hepatitis Delta International Network (HDIN) in October
HDV LIFE CYCLE

Uncoating of Virus

Transport to Nucleus

Replication

Assembly

Prenylation

Release of Progeny

HDV genome

small delta antigen

large delta antigen

prenylated LHDAg

prenyl moiety

HBsAg

Lambda Interferon

Stat

ISG Induction

Antiviral Activity

HDV genome
small HDAg
large HDAg
prenylated LHDAg
prenyl moiety
HBsAg

Jak

Lambda Interferon Receptor

Interferon

Receptor

ISG

Induction

Antiviral Activity
HDV LIFE CYCLE

Entry Inhibitors (i.e. Myrcludex-b)

Uncoating of Virus

Transport to Nucleus

Replication

Assembly

Uncoating of Virus

Release of Progeny

Cytoplasm

HDV genome

HDV genome

large delta antigen

small delta antigen

HDV LIFE CYCLE

Entry Inhibitors (i.e. Myrcludex-b)

Uncoating of Virus

Transport to Nucleus

Replication

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HDV genome

prenylated LHDAg

prenyl moiety

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Antiviral Activity

HDV genome

HBV surface antigen

large HDAg

small HDAg

Lambda Interferon Receptor

Induction

Antiviral Activity
**HDV LIFE CYCLE**

- **Uncoating of Virus**
  - HDV genome

- **Transport to Nucleus**
  - HDV genome

- **Replication**
  - large HDAg

- **Assembly**
  - Prenylation
    - prenylated LHDAg

- **Prenylation**
  - prenyl moiety
  - HBsAg

- **Release of Progeny**
  - Lambda Interferon Receptor

- **Nucleic Acid Polymers (i.e. REP 2139)**

- **ISG Induction**

- **Antiviral Activity**

- **HDV genome**
  - small HDAg
  - large HDAg
  - prenylated LHDAg
  - prenyl moiety
  - HBsAg
Uncoating of Virus

Transport to Nucleus

Replication

Assembly

Release of Progeny

HDV LIFE CYCLE

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**HDV LIFE CYCLE**

- **Uncoating of Virus**
- **Transport to Nucleus**
- **Reproduction**
- **Assembly**
- **Release of Progeny**

**Key Elements**:
- HBV surface antigen (HBsAg)
- Large HDAg
- Small HDAg
- Pre-prenylated LHDAg
- Prenyl moiety
- HDV genome

**Antiviral Activity**

- Lambda Interferon
- Jak
- Stat
- ISG Induction