Hepatitis D Treatment
Endpoints:
How Do We Measure Success in the Era of Emerging Therapies?

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Disclosure

Honoraria for consulting or speaking and/or research grants:

Abbvie, Gilead, MSD, Eiger, HepQuant, Canfite and ChemoMab
Outline

• HDV-epidemiology & clinical aspects
• Current management
• Defining suitable endpoints for clinical trials in HDV
• Review data from recently completed studies and outline of upcoming trials evaluating novel therapies
Hepatitis Delta Virus

- An incomplete RNA virus
- Co-dependent on HBV for packaging
- Dependent on host RNA polymerases for replication
- Single ORF encoding 2 non-structural proteins
- 2 patterns of infection:
  - Coinfection
  - Super infection
Epidemiology

- 15-20 million affected worldwide
- ~5% HBV infected patients
- Genotype 1-most common
- HDV is found in every country except:
  - Where it is not tested for
  - Anti-HDV tests don’t work

Recent immigration trends

Where do Europe’s migrants come from?
Total foreign-born communities by continent of origin in EU28, Top countries of origin
2016

5 million
Latin America, Caribbean
Top countries of origin:
Ecuador, Brasil

1 million
North America, Oceania
Top countries of origin:
USA

9 million
Non-EU Europe
Top countries of origin:
Ukraine, Russia, Turkey

20 million
Mobile EU citizens
Top countries of origin:
Romania, Poland, Italy, Portugal

10 million
North & Sub-Saharan Africa
Top countries of origin:
Morocco, Algeria, Tunisia, Nigeria

12 million
Asia, Middle East
Top countries of origin:
India, China, Pakistan, Syria

Source: Eurostat, European Political Strategy Centre
HDV: Most severe form of chronic viral hepatitis

Fattovich et al, Seminars in Liver Diseases 2003
Westbrook et al, J Hepatology 2014
Manesis et al, *J Hepatol* 2013

Fattovich et al, *Gut* 2000
CHD-Liver transplantation

<table>
<thead>
<tr>
<th>Table 1 Prevalence of HDV infection in Israel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samples tested, N</strong></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Age (mean± SD)</td>
</tr>
<tr>
<td>Gender (n=8744)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

*The number of samples for which this information was available

Hadassah Medical Center: 1990-2005

<table>
<thead>
<tr>
<th>Indication</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV positive</td>
<td>71</td>
<td>85%</td>
</tr>
<tr>
<td>HBV/HDV coinfected</td>
<td>12</td>
<td>15%*</td>
</tr>
</tbody>
</table>

* 18% after excluding cases where HBV was not the primary indication for liver transplantation

Milgrum Y & Saffadi R personal communication
Survival following LT for CHD

Roche & Samuel. Semin Liver Dis 2012
Current management of CHD

- No approved treatment for CHD!
- No impact of NUCs
- Pegylated IFN-Alpha
  - significant side effects
  - limited efficacy
  - patients with advanced disease not eligible
  - high long-term relapse rates

HIDIT-I

HIDIT-II


Wedemeyer H. Lancet Infect Dis 2019
Is SVR feasible with IFN-Alpha?

**HIDIT-I**
HDV Neg at W24 post treatment **28%**

**HIDIT-II**
HDV Neg at W24 post treatment **27%**

56% of patients that were HDV neg at W24 post treatment became HDV RNA pos on long-term follow up

Heidrich B. Hepatology 2014
IFN-Alpha is associated with improved long-term clinical outcomes

Manesis et al, J Hepatol 2013

HR for liver related-events in IFN-Alpha treated patients:
0.14 (0.02-0.86); p=0.033

Wranke A. Hepatology 2017
Endpoints in clinical trials in CLD

Goals of treatment
Prevent progression of liver disease and its complications
- Decompensation
- HCC
- Death

Endpoints
Surrogates markers that are reasonably likely to predict clinical benefit
SVR in Hepatitis C

Van Der Meer. JAMA 2012

HCC reduction

ESLD complications

Hepatitis B virus suppression

Wu CY Gastroenterology 2014

Su TH Liver Int 2016
Long-term NUC therapy in HBV is associated with fibrosis regression

Chang TT. Hepatology 2010

Marcellin P. The Lancet 2013
Choosing endpoints for clinical trials of novel HDV therapies

- Data on specific surrogate endpoints that are associated with long term clinical benefit is sparse
- Cure from HDV may not be feasible
- Selection of endpoints that are reasonably likely to predict clinical benefit is preferable over ideal endpoints that may not yet be achievable (HBsAg loss, SVR)
Choosing endpoints for clinical trials of novel HDV therapies

- **Measures of viral suppression**
  - ✔️ Viral log decline
  - ✔️ Virus undetectability

- **Markers of improvement in necroinflammation**
  - ✔️ ALT normalization
  - ✔️ Improved histology scores

- ✔️ Composite endpoints have advantage over singular endpoints
- ✔️ Durability of response - assessed by primary or secondary endpoints
Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy

Yurdaydın et al. J Hepatol 2017

- ≥ 2 log reduction in HDV viral load at EOT compared to baseline- target for the assessment of initial treatment efficacy with drugs currently being evaluated
### Table 1. Treatment goals for clinical trials in HBV/HDV coinfection.

<table>
<thead>
<tr>
<th>Treatment goals</th>
<th>Parameter</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic efficacy during treatment</td>
<td>Relative HDV RNA decline during treatment compared to baseline levels</td>
<td>HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity</td>
</tr>
<tr>
<td>Virologic efficacy off treatment</td>
<td>HDV RNA suppression/decline 24 weeks off-treatment and during further long-term follow-up</td>
<td>HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity</td>
</tr>
<tr>
<td>Serological efficacy-1</td>
<td>HBsAg levels (log declines and loss) at end-of treatment and off treatment</td>
<td>validated quantitative HBsAg assay (IU/ml)</td>
</tr>
<tr>
<td>Serological efficacy-2</td>
<td>Seroconversion to anti-HBs at end-of treatment and off treatment</td>
<td>validated quantitative anti-HBs assay (IU/L)</td>
</tr>
<tr>
<td>Biochemical efficacy (1)</td>
<td>ALT normalisation at the end of treatment and off-treatment</td>
<td>Validated assays (IU/L)</td>
</tr>
<tr>
<td>Biochemical efficacy (2)</td>
<td>Relative ALT declines during treatment and off treatment</td>
<td>Validated assays (IU/L)</td>
</tr>
<tr>
<td>Combined virologic and biochemical response-1</td>
<td>HDV RNA decline of 2log (or PCR negativity if baseline viral load is &lt;100 IU/ml) in combination with ALT normalisation at EOT</td>
<td>HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.</td>
</tr>
<tr>
<td>Combined virologic and biochemical response-2</td>
<td>HDV RNA decline of 2log (or PCR negativity if baseline viral load is &lt;100 IU/ml) in combination with ALT normalisation at 24 weeks off treatment and further during long-term follow-up</td>
<td>HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.</td>
</tr>
<tr>
<td>Histological efficacy – grading</td>
<td>Improvement of HAI of at least 2 points</td>
<td>Total Ishak inflammation score (A + B + C + D); 0–18 points</td>
</tr>
<tr>
<td>Histological efficacy – staging</td>
<td>No worsening of fibrosis scores</td>
<td>Ishak score (0–6 points)</td>
</tr>
<tr>
<td>Safety – Drug-specific AEs</td>
<td>AEs and SAEs</td>
<td>Severity and relation ot study drug</td>
</tr>
<tr>
<td>Safety – Disease-specific AEs</td>
<td>HBV and HDV reactivation</td>
<td>HBV DNA, HDV RNA, ALT and other liver function parameters</td>
</tr>
<tr>
<td>ProQOLs</td>
<td>Quality of life during and after end of therapy</td>
<td>EQ5, SF-36, etc.</td>
</tr>
</tbody>
</table>

### Table 2. Additional explorative endpoints for clinical trials in HBV/HDV coinfection.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Parameter</th>
<th>Readout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver stiffness</td>
<td>Liver elastography</td>
<td>e.g. fibroscan, ARFI</td>
</tr>
<tr>
<td>Serum biomarkers for inflammation and fibrosis</td>
<td>Established scores (e.g. APRI, FIB4, Delta Fibrosis score) Novel parameters</td>
<td>Serum-/Plasma tests</td>
</tr>
<tr>
<td>Intrahepatic virologic response (HDV and HBV)</td>
<td>Intrahepatic HDV RNA, hepatitis D antigen staining, HBV DNA, HBV RNA, HBV</td>
<td>Standardized virologic assays</td>
</tr>
<tr>
<td>Immune responses</td>
<td>HDV-specific T cells, HBV-specific T cells, NK cell frequency and function, soluble inflammatory mediators</td>
<td>T cell assays, flow cytometry, bead-arrays</td>
</tr>
</tbody>
</table>

AFRI, acoustic radiation force impulse; APRI, aspartate aminotransferase to platelet ratio index; cccDNA, covalently closed circular DNA; FIB4, Fibrosis-4 score; HBV, hepatitis B virus; HDV, hepatitis D virus; ProQOLs: Professional Quality of Life scales.

* Ref. 62.
Histologic Improvement following IFN-alpha therapy

Adapted from Yurdaydın et al. J Viral Hepatitis. 2008
Endpoints for phase III clinical trials

- Surrogate endpoints that are reasonably likely to predict clinical benefit
- Preferred: % of trial patients with undetectable serum HDV RNA and ALT normalization.
- Acceptable: Greater than or equal to 2 log10 decline in HDV RNA and ALT normalization

Timing of primary endpoints assessment

- The optimal timing of the primary endpoint assessment is unknown
- For therapies intended to be administered indefinitely, an on-treatment assessment after a predefined time period can be acceptable for efficacy.
- For therapies intended to be administered for a finite duration, FDA’s preferred endpoint is an off-treatment assessment of efficacy.
Novel therapeutic targets for HDV

- No RNA polymerase to target
- HDV is dependent on HBsAg
- Inhibition of viral entry (Micrludex-B)
- Interference in viral assembly (Lonafarnib)
- Interference in HBsAg release (Nucleic acid polymers)
- Immunomodulation (pegIFN-Lambda)

Adapted from Gilman C et al. World J Gastroenterol 2019
Myrcludex B

- First-in-class entry inhibitor for treatment of chronic HBV and HDV
- Synthetic 47 amino acid, N-acylated preS1 lipopeptide
- Targets Na-taurocholate co-transporting polypeptide (NTCP)
- Exclusively targets parenchymal liver cells
- Blocks receptor functions of NTCP and HBV/HDV virus entry
Myrcludex B - Pilot study

Primary endpoint: HBsAg decrease at W12
Not met

- **Myr B**: HDV RNA -1.67 log, 2 pts HDV RNA Neg
- **Myr B + PEG IFN**: HDV RNA -2.59 log, 5 pts HDV RNA Neg
- **PEG IFN**: HDV RNA -2.17 log, 2 pts HDV RNA Neg

Primary endpoint: 2 log decline HDV RNA or RNA Neg at Wk 24

Median RNA log change from baseline:
- Myr B 2mg: -1.75
- Myr B 5mg: -1.60
- Myr B 10mg: -2.70
- TDF: -0.18

Conclusion:
- ALT levels normalize in 40-50% (not dose-dependent)
- HBsAg does not change
- Bile acids increase without pruritus

* Wedemeyer et al. EASL 2018

Myrcludex B- Open-label phase 2b study

Median HDV RNA levels

[Graph showing median HDV RNA levels over time]

Primary endpoint:
2 log decline HDV RNA or RNA Neg at Wk 24
**MYR 203 phase 2-End of study results**

Primary endpoint: Undetectable HDV RNA at week 72

Conclusions:
- Myr B monotherapy is safe and induces HDV RNA AND ALT reduction on Rx, but most patients relapse
- Combo therapy shows improved efficacy and may induce cure in a subset of patients

*Wedemeyer et al. EASL 2019*
Primary endpoint:
Undetectable HDV RNA at W72
W48 results presented

Conclusions:
• 10mg BLV monotherapy is safe and more suitable for maintenance therapy.
• As shown in lower doses, strong synergism with pegIFN
• No advantage in HBsAg response over lower doses
• Prolonged Rx (2-3y) will be studied in phase III trials
Mycludex B for HDV: Phase 3 Pivotal Trial MYR301
-> Start Q4 2018

Comparison for primary endpoint

Arm A (n=50)  observational  10mg MyrB + NA  follow up

Arm B (n=50)  10mg MyrB + NA  follow up

Arm C (n=50)  2mg MyrB + NA  follow up

week 0  week 48  week 144  week 192

Composite primary endpoint:
undetectable HDV RNA or >2log decline as well as ALT normalization at week 48

- Only patients with treatment indication for chronic HBV infection (EASL/AASLD guidelines) will be treated with NA

ClinicalTrials.gov Identifier: NCT03852719
Phase 3 Study of Bulevirtide in Patients With CHD

A Multicenter, Open-label, Randomized Phase 3 Clinical Study to Assess Efficacy and Safety of Bulevirtide in Patients With Chronic Hepatitis Delta

Primary outcome measure
Combined response: Undetectable HDV RNA or decrease by $\geq 2 \log_{10}$ IU/ml from baseline +
ALT normalization at week 48 weeks

ClinicalTrials.gov Identifier: NCT03852719
Lonafarnib

- Prenylation- lipid modification that involves addition of prenyl lipids to proteins resulting in promotion of membrane association and protein–protein interactions

- Small molecule, oral, prenylation inhibitor that inhibits attachment of prenyl lipid farnesyl to LHDAg

- Disruption of prenylation of LHDAg prevents the interaction with HBsAg and formation of secreted particles

- POC study- 14 pts, 28 days, LNF 100mg/200mg vs placebo Significant HDV RNA log decline, GI side effects with higher doses, no evidence of virological resistance
Lonafarnib phase 2 program

Identifying Dose and Regimen for Registration N=129

- **Proof of Concept**
  - Monotherapy \( N = 14 \)
- **LOWR HDV – 1**
  - \( \pm \) RTV or PEG IFN \( \alpha \) \( N = 15 \)
- **LOWR HDV – 2**
  - Dose Finding +/- PEG IFN \( \alpha \) \( N = 58 \)
- **LOWR HDV – 3**
  - QD Dose \( N = 21 \)
- **LOWR HDV – 4**
  - Dose-Escalation \( N = 15 \)
LOWR HDV-1

- Assess tolerability and viral response of different doses of LNF as monotherapy or in combination with RTV or PEG-IFNa
- Primary endpoint: HDV-RNA decline between baseline and end of treatment (8/12 weeks)
- Combo therapies – significant viral decline and ALT normalization, improved GI tolerance

Viral rebound in all but 2 pts who had ALT flares → HDV UD → HDV UD/LLOQ

Yurdaydın. Hepatology 2017
**LOWR HDV – 2: “Dose Finding” Study**

**Aim:** Identify optimal combination regimens of LNF and RTV ± PEG-IFNα with efficacy and tolerability for longer term dosing

**Primary endpoint:**
HDV RNA decline from baseline $\rightarrow$ EOT

**Summary:**
All-oral LNF +RTV regimens - 39% viral response at W24
Addition of PEG IFN to LNF +RTV - 89% viral response at W24
Post Rx ALT flares followed by HDV RNA negativity
Mild-moderate GI side effects with LNF 25mg/50mg +RTV

**Conclusions:**
All-oral regimens - viable option for patients with low viral load
Combo therapy results in highest response rate

*Yurdaydin et al. EASL 2018*
LOWR-3 – Once daily dosing study

Primary objective
-To assess the antiviral effects and safety of once daily RTV boosted LNF, in patients with chronic HDV infection

Treatment was safe and generally well tolerated
Response guided therapy beyond 6 months may lead to viral clearance
In a subset of patients

Koh et al. EASL 2017

LOWR-4 Dose Escalation study

Primary Objectives
- Dose-escalation / maintenance up to LNF 100 mg BID + RTV for 24 weeks
- Safety and tolerability of LNF + RTV dose-escalation for 24 weeks
- HDV-RNA decline over 24 weeks

Wedemeyer et al. EASL 2017
**D-LivR**: PHASE 3 GLOBAL STUDY

**Delta-Liver Improvement and Virologic Response in HDV**

### Run-In
- 12-24 weeks
- **Nuc**
  - All-Oral
    - Lonafarnib 50 mg BID
    - Ritonavir 100 mg BID
- **N = 175**

### On-treatment
- 48 weeks
- **Nuc**
  - Combo
    - Lonafarnib 50 mg BID
    - Ritonavir 100 mg BID
    - PEG IFN-alfa-2a
- **N = 125**

### Post-treatment
- 24 weeks
- **Nuc**
  - Mono
    - PEG IFN-alfa-2a
- **N = 50**

### Follow Up
- **N = 50**

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**Primary Endpoint at Week 48**
- $\geq 2$ log decline in HDV RNA
  + Normalization of ALT

**Secondary Endpoint at Week 48**
- Histologic improvement
  - $> 2$-point improvement in HAI inflammatory score
  - No progression in fibrosis
- Improvement of fibrosis

ClinicalTrials.gov Identifier: NCT03719313
Pegylated Interferon Lambda

• 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
• Greater than 3,000 patients in 17 clinical trials (HCV / HBV)
• Comparable antiviral activity with less of the typical IFN alfa related side effects*

* Chan, HLY et al, J Hepatology 2016
LIMT: Phase 2 Lambda Monotherapy Study

Objectives:
- Evaluate safety and tolerability of Lambda monotherapy for 48 wks
- Efficacy endpoint: Change in HDV RNA from BL to Week 48 and Week 72

Etzion et al. EASL 2019
LIMT: Phase 2 Lambda Monotherapy Study

Conclusions:
- Durable virologic response of Lambda (36%) compares favorably to historic rates for Alfa 180 μg (28%)
- Better tolerability than Alpha
- Histologic improvement?

Etzion et al. AASLD 2019
LIFT HDV Study

- Phase 2a, Open-Label Study
- Lambda 180 mcg/w+ LNF 50mg/RTV 100 bid for 24 weeks
- Primary Endpoints:
  >2 log decline HDV RNA at W24
  Safety of triple combination for 24 weeks

Summary
- Therapy with LMD/LNF/RTV was relatively safe in most patients for up to 6 months.
- Per protocol discontinuation of triple combination therapy was mostly due to known side effects related to peginterferon lambda.

Koh et al. AASLD 2019
Nucleic acid polymers (NAPs) are oligonucleotides with broad spectrum in vitro antiviral activities.

- Proposed to bind to amphipathic protein structures.

1. Inhibition of HBV SVP assembly/secretion and HDV envelopment
   - Allows host-mediated clearance of HBsAg/HDV
   - Blocks release of HDV

2. Interaction with S-HDAg
   - Potential upstream inhibition of HDV RNA synthesis

3. Interaction with L-HDAg
   - Potential upstream inhibition of HDV RNP assembly
REP 2139-Ca / Pegasys™ Combination Therapy in HBV / HDV Co-infection

- **Rapid HBsAg clearance prior to pegIFN**
  - Universal and rapid HBV RNA response
    - Target not detected in 11/12 participants during therapy
    - Even in participants with moderate HBsAg response
    - Likely due to upstream direct effects against HDV replication

- **Completed treatment and 3.5 years of follow-up**
  - Clinical response
    - Normal ALT: 8/11 (73%)
    - Normal / declining liver median stiffness: 7/11 (64%)
  - HBsAg response
    - < 1 IU/ml: 6/11 (55%)
    - ≤ LLOQ (0.05 IU/mL): 5/11 (42%)
    - Seroconversion: 4/11 (36%)
  - HDV RNA response
    - > 2 log₁₀ reduction from baseline: 9/11 (82%)*
    - TND: 7/11 (64%)
  - *2 participants maintaining 2.67 and 2.12 log₁₀ HDV RNA reduction from baseline at 3.5 years follow-up did not maintain normal liver function during follow-up.

- **Functional cure of HDV at 3.5 years of follow-up**
  - (HDV RNA TND, ALT normal)
    - HBV DNA response
      - ≤ 2000 IU/mL: 7/7 (100%)
      - Target not detected (TND): 5/7 (71%)
    - HBV virologic response
      - Virologic control HBV (HBV DNA ≤ 2000 IU/mL, normal ALT): 3/7 (43%)
      - Functional cure HBV (HBsAg < LLOQ, HBV DNA TND, normal ALT): 4/7 (57%)
      - HBV clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC): 7/7 (100%)
    - On-therapy flare
      - Asymptomatic transaminase flare while HBsAg ≤ 1IU/mL: 7/7 (100%)
Objectives:
Assessment of safety tolerability and efficacy

Endpoints:
- HBsAg and HDV RNA loss during therapy
- HBsAg seroconversion
- Therapeutic transaminase flares

- Functional cure of HBV & HDV >6 months following treatment cessation

Tentative starting date: Tentative Q4 2020
In summary

• CHD is a severe disease for which current management is unsatisfactory
• Data on surrogate endpoints predicting long term clinical benefit is sparse
• Clinical trials assessing novel therapies for HDV rely on endpoints that are reasonably likely to predict clinical benefit
• Long term follow up will be required to establish the validity of these endpoint as surrogate markers of clinical benefit
• Therapies allowing viral suppression/elimination are on the horizon
Thank You!

Leaders have to be dealers in hope.

~ Napoleon Bonaparte

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