Hepatitis D

Challenges in 2018

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Disclosures

Honoraria for consulting or speaking (last 5 years):
Abbott, AbbVie, Abivax, BMS, Boehringer Ingelheim, Eiger, Gilead, JJ/Janssen-Cilag, Medgenics, Merck/Schering-Plough, MyrGmbH, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViiV

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Abbott, Abbvie, BMS, Gilead, Merck, Novartis, Roche, Roche Diagnostics, Siemens
The Hepatitis D Virus

HDV-RNA
- The smallest of all animal viruses
- Highly paired – rod like structure
- No enzymes but Ribozymes
- Only encodes S-HDAg

HBsAg
- HBsAg particles can self assemble
- HBV: 1 virion x 10^3-10^6 particles

HDAg
- 2 forms: S-HDAg and L-HDAg
- S-HDAg: ↑ replication
- L-HDAg: ↑ assembly (↓ replication)

Is HDV just one example of a frequent phenomenon?

Simultaneous Co-Infection
- Acute HBV
- Acute HDV
  - 95% recovery
  - More frequent fulminant

HDV Super-Infection
- Acute HDV
  - Chronic Hepatitis B
  - 90% chronic
  - More severe disease
♀ 42 years, born in Russia
HBsAg positive
(known since >10 years)
ALT 64 U/l; AST 52 U/l
HBV DNA 79 IU/ml
Anti-HDV positive
HDV RNA $7.6 \times 10^6$ cop/ml

Histology: Liver cirrhosis

HDV suppresses HBV

Lutterkort et al. Liver International 2017
Non-invasive fibrosis markers developed for HCV do not work well in hepatitis delta

A non-invasive fibrosis score for hepatitis D (DFS):
Albumin, gGT, CHE, Age

1 (if Alb < 1.19$^{(\text{ULN})}$) + 1 (if gGT > 0.5$^{(\text{ULN})}$) + 1 (if CHE < 1.46$^{(\text{ULN})}$) + 1
(if age > 42).

Lutterkort et al., Liver International 2017
HDV coinfected patients more often develop clinical complications

High frequency of clinical complications in HIV+ patients with hepatitis delta

Beguelin et al., J Hepatol 2017 (66:297-303)
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Heterogeneity of hepatitis delta world-wide: the HDIN network

- The Hepatitis Delta International Network (HDIN)
- 1579 anti-HDV+ or HDV-RNA+ patients from 15 countries

Wranke et al., Liver International 2017 epub
Every HBsAg-positive patient should be tested once for anti-HDV.

... e.g. only 8.5% of HBsAg-patients were tested for anti-HDV in a USA–VA cohort. Kushner et al. J Hepatol Sept. 2015

Diagnosis of HDV infection
Diagnostic Steps in Delta Hepatitis

- HBsAg+ → Anti-HDV+ → HDV-RNA-pos
- HDV-RNA-neg

The need to standardize methods to monitor HDV RNA
High variability between HDV PCR assays and labs

Le Gal et al., Hepatology 2016
Different HDV genotypes are associated with different clinical outcomes

Su et al, Gastroenterology 2006
Pathogenesis of hepatitis delta

NK cells in HBV and HDV infection differ in phenotype and function and are associated with response to PEG-IFNa therapy

Lunemann, JID 2014

Lunemann, GUT 2015
Weak HDV-specific T cell responses can be restored by Third Signal Cytokines

Identification of patients with a higher risk for disease progression
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Platelet count 93.000/µl
INR 1.2; bilirubin normal

“BEA-B” Treatment should be recommended

Calle Serrano et al. J Viral Hepatitis 2014
The Hepatitis Delta Virus:
No viral enzyme → no direct acting antiviral

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Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% Sustained HDV RNA clearance

**Figure 1.** Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

... and prolonging treatment to 2 years + combination with tenofovir?
The *Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2*

### Stratification:
- Country
- Previous therapy
- Gender

#### Treatment Groups:
- **PEG-Interferon alpha-2a 180µg oiw + Placebo**
- **PEG-Interferon alpha-2a 180µg oiw + Tenofovir disoproxilfumarat 245mg daily**

#### Primary efficacy endpoint:
HDV RNA negativity Week 96

#### Follow-up:
- 96 weeks
- 5 years FU

N=61

N=59

### HDV RNA response until week 120 (Intent-to-treat analysis)

#### % of patients HDV RNA negative

- **Treatment**
- **FU**

#### Relapse:
- PEG-IFNa-2a + Tenofovir:
  - Relapse 11/25 (44%)
- PEG-IFNa-2a +Placebo:
  - Relapse 8/20 (40%)

#### HDV RNA Clearance after Therapy
- Neg post Tx 1 patient
- Neg post Tx 3 patients

#### Week 120:
- 24 w post Tx

Wademeyer, Yurdakul et al. EASL 2014
Treatment with PEG-IFNa2a

HDV RNA neg week 24
HDV RNA neg week 48
HDV RNA neg Fu-w 24
HDV RNA Fu-w 60 1.7 x 10^5 cop/ml

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Late Relapses after initial response!: 
No „SVR” in hepatitis delta!

Long Term Virological Response

Late Relapse

Heidrich et al., Hepatology 2014

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HDV RNA neg Fu-w 24
HDV RNA FU-w 60
1.7 x 10^5 cop/ml
NA-monotherapy?
Longterm tenofovir therapy in HIV+/HBV+/HDV+ patients

Clinical effects of antiviral therapy
Improved outcome of hepatitis delta in IFNa-treated patients

Wranke et al., Hepatology 2017;65:414-425

Patients experiencing an HDV RNA loss had a better clinical long-term outcome

Wranke et al., Hepatology 2017;65:414-425
Current Management of Hepatitis Delta

- Patients with a very mild course can be identified (possibly not requiring immediate treatment)
  Clinical markers: Calle Serrano J Viral Hepatitis 2014
  Anti-HDV IgM Levels: Wranke et al., PlosOne 2014
  NK cell responses: Lunemann et al., GUT 2015

- PEG-IFNa remains the only effective treatment option against HDV
  - stopping rules week 24: Keskin et al., CGH 2015
  - however, long-term follow-up is required
  - my recommendation: Treat Bea-B patients

- Treat HBV according to hepatitis B guidelines

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Any novel clinical trials?
HDV Replication

Hughes, Wedemeyer, Harrison Lancet 2011

Blocking of subviral particle release

Hughes, Wedemeyer, Harrison Lancet 2011
Nucleic Acid Polymers for HDV infection

*Rep-3129: blocking particle release*

Bazinet et al., **Lancet Gastroenterol & Hepatol** 2017

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Prenylation inhibition

Blocks virion assembly and packing of viral particles

Hughes, Wedemeyer, Harrison **Lancet** 2011
Lonafarnib for HDV infection
LOWR-HDV-4 (PS-039)

Week 48:
% with > 2 log decline: 3/15 (20%)

Pt 14: HDV-RNA < LLOQ

Entry Inhibitor „Myrcludex“

Hughes, Wedemeyer, Harrison Lancet 2011
Myrcludex B 202 Trial:
Dose dependent asymptomatic increase in bile acids

- Myrcludex B blocks bile acid transporter NTCP
- 23% of patients had elevated bile acids already at BL visit
- Asymptomatic dose-dependent increase in bile acids was observed at week 24 in:
  - 50% (2mg),
  - 74% (5mg),
  - 91% (10mg)
  - 19% (TDF)

Primary endpoint:
2 log HDV RNA decline or negative week 24

Median HDV RNA levels

Median RNA log10 change to BL
MyrB 2mg: -1.75
MyrB 10mg: -2.70
MyrB 5mg: -1.60
TDF: -0.18
Myrcludex B 202 Trial: ALT decline is not dose-dependent

ALT normalization (week 24)

- % ALT normalization
- MyrB 2mg vs TDF * p=0.0013
- MyrB 5mg vs TDF ** p=0.0002
- MyrB 10mg vs TDF ** p=0.0023

Mean ALT levels

- 10 mg MyrB / TDF
- 5 mg MyrB / TDF
- 2 mg MyrB / TDF
- TDF

Myrcludex B 202 Trial: no effects on HBsAg

Wedemeyer et al. AASLD 2017
Summary

- PEG-IFNa is currently the only treatment option for HDV infection
- HBV entry inhibition, prenylation inhibition and block of particle formation may represent new treatment options
- Novel strategies to achieve HBsAg clearance need to be explored in hepatitis delta!

...and if you want to be more involved in hepatitis delta