Current & new treatment options in chronic hepatitis D

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Lab of Internal Medicine
Larissa Medical School
Thessaly University
The smallest among mammalian viruses

35-37 nm diameter virus featuring a small single-stranded, circular RNA genome of 1672-1697 nucleotides

Taylor, WJG 2014
How easy is to treat chronic hepatitis delta patients?
A case report - 26 years old (I)

- Initial evaluation at our centre at 2014
- Origin: Romania
- CHB known from the age of 12 years (2000) – no follow-up
- 5 years before transfused due to ferrum deficiency anaemia at a General Hospital of Greek NHS (no other guidance)
- Alcohol: no - IVDU: no
- AST 55 IU/L, ALT 49 IU/L, γGT 59 IU/L, ALP 100 IU/L (UNL 120)
- INR 1.06, ALB 4.5 g/dL, PLT 160000/μL
How easy is to treat chronic hepatitis delta patients?
A case report - ♀ 26 years old (II)

- HBsAg (+) – antiHBs (-) – antiHBc (+) – HBeAg (-) – antiHBe (+)
- anti-HDV (+) – (evaluated for 1st time at 2014 !!!)
- anti-HCV (-)
- anti-HAV (-) → immunization initiated
- anti-HIV (-)
- HDV-RNA: 567657 copies/ml
- HBV-DNA: negative
- US: without focal lessions
- **Fibroscan**: 17.6 kPa (Metavir F4)
- **Liver Biopsy**: F3F4 – A1A2
- **Peg-IFN-α-2a initiated at SEP 2014**
How easy is to treat chronic hepatitis delta patients?
A case report - ♀ 26 years old (III)

Baseline
PegIFN start
SMA pos

ALT (IU/L)
HBV DNA (IU/ml)
HDV RNA (c/ml)
IgG (mg/dL)

month 8
biopsy: typical for AIH
ANA pos, SMA pos
PegIFN stop
Prezolon+MMF start
TDF start

month 14
PegIFN restart
Prezolon+MMF
TDF

ALT, 49
HDV RNA, 547675
HBV DNA, 0

ALT, 533
IgG 2010
ALT, 296
IgG, 1365

ALT, 30
HDV RNA 5290
HBV DNA, 26
ALT, 28

ALT, 42
HDVRNA, 677635
IgG, 1051
IgG, 1160
IgG, 1810

ALT, 28
HDV RNA, 0
HBV DNA, 0

ALT, 49
HDV RNA, 547675
HBV DNA, 0

ALT (IU/L)
HBV DNA (IU/ml)
HDV RNA (c/ml)
IgG (mg/dL)
Treatment of chronic hepatitis D
Alpha-Interferon
...the only available treatment

End of treatment
End of follow-up

Rosina 1989: 33% (8%)
Farci 1994: 71% (0%)
Madejon 1994: 66% (9%)
Castelnau 2006: 50% (0%)
Niro 2006: 43% (43%)

alpha-interferon
pegylated - IFNα
Peg-Interferon plus Adefovir vs. Either Drug Alone for Hepatitis Delta

Heiner Wedemeyer, M.D., Cihan Yurdaydın, M.D., George N. Dalekos, M.D., Andreas Erhardt, M.D., Yılmaz Çakaloğlu, M.D., Halil Değertekin, M.D., Selim Gürel, M.D., Stefan Zeuzem, M.D., Kalliopi Zachou, M.D., Hakan Bozkaya, M.D., Armin Koch, M.D., Thomas Bock, M.D., Hans Peter Dienes, M.D., and Michael P. Manns, M.D., for the HIDIT Study Group

Treatment Options for Hepatitis Delta

- HBV polymerase inhibitors are ineffective against HDV
- 48 weeks of PEG-IFNa leads to HDV RNA negativity in 25%-30%
- PEG-IFNa + adefovir may have advantages in HBsAg reduction

Wedemeyer, NEJM 2011
However late relapses are the rule...

Among the 16 patients with SVR who underwent long-term follow-up evaluation, 9 patients (56%) experienced relapse of HDV replication, including 2 of the 5 patients negative at W24 of IFN therapy.
No benefit from new NUCs
No benefit from treatment prolongation

HiDiT-2 Study

- prolonged administration of PEG-IFNα-2a±TDF is **safe** in HDV-infected patients
- **similar efficacy** concerning HDV RNA suppression, HBsAg reduction, ALT normalisation
- more than one third of patients experience a post-treatment **relapse**
For how long should I treat chronic hepatitis delta patients?

Resolution of CHD infection after five years of PEG-IFN + ADV: Lessons from a case report

Is there any benefit treating chronic hepatitis D patients with interferon?

In HDV co-infected patients, the effect of interferon was significant (HR = 0.14; 95% CI (0.02–0.86), p = 0.033), indicating a reduction of liver-related events in treated cases.
Treatment with Peg-IFN is equally effective in cirrhotic CHD patients

Pegylated interferon-based treatment in patients with advanced liver disease due to chronic delta hepatitis

No difference in responses
More frequent adverse events

Kabacam, Turk J Gastroenterol 2012.
Treatment monitoring - The role of HDV RNA

Association Between Level of Hepatitis D Virus RNA at Week 24 of Pegylated Interferon Therapy and Outcome

Onur Keskin,* Heiner Wedemeyer,† Ali Tüzün,* Kalliopi Zachou,§ Xheni Deda,* George N. Dalekos,§ Benjamin Heidrich, † Selcen Pehlivan, ‡ Stefan Zeuzem, ‡ Kendal Yalçın, † Selim Gürel,** Fehmi Tabak, †‡ Ramazan Idilman,* Hakan Bozkaya,* Michael Manns, † and Cihan Yurdaydın*,$$

- HDV RNA (-) at week 24 of treatment —> PPV for Response 71%

- HDV RNA decline < 1 log at week 24 of treatment w/o any HBsAg decline —> PPV for Null Response 83%

- HDV RNA decline > 2 log at week 24 of treatment —> NPV for Null Response 95%

Keskin, Clinical Gastroenterology & Hepatology 2015
Treatment monitoring - The role of HBsAg

Lamivudine

IFNα

HDV RNA neg: 5/21 patients; 2 cleared HBsAg

Manesis, Antivir Ther 2007
Treatment monitoring - The role of HBsAg

Optimized HBsAg titer monitoring improves interferon therapy in patients with chronic hepatitis delta

Stopping rule
HBsAg titer < 0.5 IU/ml (neg)
Liver Transplantation: The last solution

- Rapid and Parallel Decline of HDV RNA and HBsAg after Liver Transplantation....
- Rates of recurrent HBV-HDV infection are lower than 5% using HBIG and antiviral prophylaxis in combination

Treatment of chronic hepatitis D
HBsAg envelope

Towards New HDV Treatment Targets (I)

L-HBsAg is necessary to assemble infectious particles of delta virus

Lessons from HDV Life Cycle
Towards New HDV Treatment Targets (II)

*human sodium taurocholate cotransporting peptide
**heparin sulphate proteoglycans

reviewed in Alfaiate, Antiviral Res 2015
Lessons from HDV Life Cycle
Towards New HDV Treatment Targets (III)

reviewed in Alfaiate, Antiviral Res 2015
Genome & Antigenome Forms of HDV RNAs Towards New HDV Treatment Targets (IV)

- virus ribozyme:
  - self-cleaving
  - self-ligation

reviewed in Alfaiate, Antiviral Res 2015
Hepatitis Delta Antigen (HDaG)  
Post-translational modifications  
Towards New HDV Treatment Targets (V)

prenylation (farnesylation)  
phosphorylation  
methylation  
acetylation

prenylation of the last four amino acids of the L-HDaG (CXXX box) is required for the interaction of the HDaG with the HBsAg to form the virion.

reviewed in Alfaiate, Antiviral Res 2015
Emerging Therapies

**antisense oligonucleotides**
- Lutgehetmann M, 2012
- Koh, Lancet Infect Dis 2015
- Chan, Clin Exp Pharmacol Physiol 2006
- Li, Zonghua Ganzangbing Zazhi 1999

**entry inhibitors (Myrcludex)**
- Lutgehetmann M, 2012
- Koh, Lancet Infect Dis 2015

**prenylation inhibitors**
- Glenn JS, 2006
Emerging Therapies

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  - Lutgehetmann M, 2012
  - Koh, Lancet Infect Dis 2015

**prenylation inhibitors**

Glenn JS, 2006
Emerging Therapies
Oral prenylation inhibition with Lonafarnib

Phase 2A study
28 days administration in 14 pts

22 patients with +HDVAb screened

8 patients excluded
4 HDV RNA undetectable
3 did not complete preTx evaluation
1 with hepatocellular carcinoma

14 patients with +HDV RNA enrolled

8 patients assigned to group 1 (lonafarnib 100 mg twice daily)
6 received masked treatment
2 received masked placebo

6 patients assigned to group 2 (lonafarnib 200 mg twice daily)
2 received open-label treatment
2 received masked placebo
4 received masked treatment

Koh, Lancet Infect Dis 2015
Emerging Therapies
Oral prenylation inhibition with Lonafarnib

phase 2A study
28 days administration in 14 pts

HDV RNA decline
-0.13 log
-0.73 log
-1.54 log

Koh, Lancet Infect Dis 2015
A biphasic decline of serum HDV RNA during therapy was characterised in all patients given lonafarnib.

**LONAFARNIB vs. PEG-IFN**

- Effectiveness: 95% vs. 96%
- Time (median): 12 days vs. 25 days
Emerging Therapies
Oral prenylation inhibition with Lonafarnib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo group (n=4)</th>
<th>Group 1 (n=6)</th>
<th>Group 2 (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation of therapy due to an adverse event</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Serious adverse events</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Common adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (25%)</td>
<td>2 (33%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>3 (50%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>1 (17%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Abdominal bloating/dyspepsia</td>
<td>1 (25%)</td>
<td>1 (17%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Weight loss &gt;2 kg</td>
<td>0</td>
<td>1 (17%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (25%)</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
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<td>Testicular pain</td>
<td>0</td>
<td>1 (17%)</td>
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<tr>
<td>Lightheadedness</td>
<td>1 (25%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fatigue</td>
<td>0</td>
<td>1 (17%)</td>
<td>1 (17%)</td>
</tr>
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</table>

Data are n (%).

Table 3: Treatment discontinuations and adverse events in treatment groups

Emerging Therapies
Lonafarnib plus Ritonavir boosting

- 15 HDV pts in Turkey treated with oral lonafarnib for 8 weeks
  - 200/300mg bid vs. 100mg bid + PEG vs. 100mg OD + ritonavir

Log decline HDV RNA

Ritonavir boosting increased efficacy and reduced GI side-effects

Yurdaydin, O118 EASL 2015. Dahari, LP36 EASL 2015
Emerging Therapies

**antisense oligonucleotides**
Chan, Clin Exp Pharmacol Physiol 2006
Li, Zonghua Ganzangbing Zazhi 1999

**entry inhibitors (Myrcludex)**
Lutgehetmann M, 2012
Koh, Lancet Infect Dis 2015

**prenylation inhibitors**
Glenn JS, 2006
Emerging Therapies
Blocking viral entry (HBV/HDV entry) with Myrcludex B
Emerging Therapies
Blocking viral entry (HBV/HDV entry) with Myrcludex B
A Phase 2a clinical trial

Randomization into 3 treatment arms (n = 24), 8 patients per arm

- Myr B: 2 mg/day, s.c. for 24 weeks followed by PEG-IFNα for 48 weeks; 24 weeks follow up
- (Myr B: 2 mg/day, s.c. + PEG-IFNα) for 24 weeks followed by PEG-IFNα for 24 weeks; 24 weeks follow up
- PEG-IFNα for 48 weeks; 24 weeks follow up

Endpoints

- Safety and tolerability
- Biochemical response (ALT)
- Virological response (HDV-RNA, HBV-DNA, HBsAg)
- Immunogenicity
- Bile salt elevations
Emerging Therapies
Blocking viral entry (HBV/HDV entry) with Myrcludex B
A Phase 2a clinical trial

Summary and Conclusion

- Myrcludex B alone or in combination with IFNα was well tolerated.
- No SAEs during therapy, good safety profile (even at oversaturating concentrations (10 mg/d))
- ALT normalization in HBV and HDV patients under Myrcludex B monotherapy.
- HDV serum DNA decline > 1 log10 in 6/7 patient under mono- and 7/7 under Myrcludex B/IFNα combination therapy.
- Negativation in 5/7 patients under Myrcludex B/IFNα combination therapy.
- No significant effects on HBsAg levels.
- Moderate bile salt increase at 2 mg Myrcludex B dosing.

Urban, AASLD 2014
Emerging Therapies

entry inhibitors (Myrcludex)

Lutgehetmann M, 2012
Koh, Lancet Infect Dis 2015

antisense oligonucleotides

Chan, Clin Exp Pharmacol Physiol 2006
Li, Zonghua Ganzangbing Zazhi 1999

prenylation inhibitors

Glenn JS, 2006
Emerging Therapies
Direct RNA interference therapy

HDV stable cell line Huh7-D12 cells (1) were treated with a single dose of HDV siRNA-LNP. HDV RNAs were measured by QuantiGene branched DNA (bDNA) assay and HDV antigen proteins were quantified by ELISA.
Emerging Therapies
Direct RNA interference therapy

Durable Reduction of HDV RNA Observed with a Single Dose of HDAg Targeting siRNA. Huh7-D12 cells were treated with 20 ng/mL single dose of siRNA-LNP targeting different sites in HDAg mRNA region. Inhibition of HDV negative-strand (A) and positive-strand (B) RNA levels was observed throughout the 21-day duration of the study.

Xin, Arbutus Biopharma, Canada (AASLD 2015)
A NAP named REP 2139-A is proposed to prevent formation of HBsAg subviral particles thereby unmasking an underlying pre-existing anti-HBsAg (anti-HBs) response.
Emerging Therapies
Nucleic Acid Polymers (NAPs) in CHD

- block HDV entry
- block HDV production from subviral particles – related assembly mechanism
- restore host immune response
- “liberated” anti-HBs directly target HDV
Emerging Therapies
Nucleic Acid Polymers (NAPs) in CHD

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

Results: (1) HBsAg

Follow-up 4, 12 and 24 wks

Vaillant, EASL 2015, Vienna. #LO2
An expertise laboratory is necessary to treat chronic hepatitis D patients...

No reliable and standardised commercial assays
<table>
<thead>
<tr>
<th>Samples</th>
<th>Genotype</th>
<th>LAB A technique</th>
<th>LAB B technique</th>
<th>LAB A technique</th>
<th>LAB B technique</th>
<th>Roche kit</th>
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<td>4.7</td>
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<tr>
<td>7</td>
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<td>8</td>
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<td>16</td>
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<td>4.7</td>
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<tr>
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<td>19</td>
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</table>
An expertise laboratory is necessary to treat chronic hepatitis D patients...

In-house methods in reliable reference laboratories

Department of Medicine and Research Laboratory of Internal Medicine
Larissa Medical School, Thessaly University

- Cobas TaqMan 48 (Roche)
  - Sensitivity: 10 c/ml
  - Specificity: 100%
  - Dynamic range: $10^2$-$10^8$ c/ml
  - Inter-assay variability: 1.2-2.7 Log$_{10}$ % CV
  - Intra-assay variability: 2.2-5.1 Log$_{10}$ % CV

Gatselis & Zachou 2012
An expertise laboratory is necessary to treat chronic hepatitis D patients...

In-house methods in reliable reference laboratories

Department of Medicine and Research Laboratory of Internal Medicine
Larissa Medical School, Thessaly University

<table>
<thead>
<tr>
<th>Panel 2</th>
<th>Dilution of the HDV WHO Standard (5.76 Log10 IU/mL)</th>
<th>F-NRC</th>
<th>University of Thessaly (Greece)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1:100</td>
<td>3.84</td>
<td>3.93</td>
</tr>
<tr>
<td>B</td>
<td>NC</td>
<td>not detected</td>
<td>not detected</td>
</tr>
<tr>
<td>C</td>
<td>1:10</td>
<td>4.64</td>
<td>4.59</td>
</tr>
<tr>
<td>D</td>
<td>1:10</td>
<td>4.81</td>
<td>4.41</td>
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<tr>
<td>E</td>
<td>1:100</td>
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<tr>
<td>F</td>
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<td>4.43</td>
</tr>
<tr>
<td>G</td>
<td>NC</td>
<td>not detected</td>
<td>not detected</td>
</tr>
<tr>
<td>H</td>
<td>1:100</td>
<td>3.92</td>
<td>3.89</td>
</tr>
</tbody>
</table>

Mean WHO-IS Value

<table>
<thead>
<tr>
<th>Conversion factor (c/ml to UI/ml)</th>
<th>Lab n°24</th>
<th>Lab n°9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean WHO-IS Value</td>
<td>5.85</td>
<td>5.69</td>
</tr>
<tr>
<td>0.98</td>
<td></td>
<td>1.01</td>
</tr>
</tbody>
</table>

1st International Quality Control for HDV RNA Viral Load Quantification (2013-2014)
Take Home Messages

1. Difficult to treat CHD patients
2. Pegylated Interferon is the only licensed treatment
3. “SVR” rates about 25-30%
4. “Long-term” response even less; relapses are the rule
5. No established stopping rules (HDV RNA & HBsAg)
6. Promising emerging direct acting therapies, but there is a great distance still to be covered
7. An expertise laboratory is needed when you treat CHD
Thank you for your attention!