HDV HBV co-infection: Update on New Drugs

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I have received consultancy and/or lecture fees from AbbVie, BMS, Gilead, Roche, Merck, Boehringer Ingelheim, Janssen, and Novartis, and has received grants from BMS and Roche.
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
HBcAg IHC in CDH

Nuclear localization

No correlation with liver injury, even in HBV-HDV co-dominant cases

Kabaçam et al, Liver Int 2013
HDAG IHC in CDH

HDAG display (+) correlation with ALT and HBsAg levels

Kabaçam et al, Liver Int 2013
Female patient living in Sweden, migrated from Uzbekistan

- ALT: 78, AST 66
- GGT and Alkalen Phosphatase: normal
- HBsAg (+), HBeAg negatif
- Anti HCV & HIV: negative
- HBV DNA 480 IU/mL
- Hb, WBC normal, platelets: 176 000
- Height: 1.63m; weight: 92 kg
- BMI: 34.6
Diagnosis:

İnactive HBsAg carrier + NASH

Recommendation:
Diet + exercise; No need to treat HBV

Control visit every 3 months

3 x control visits, she loses some weight
Enzymes not much affected
The patient is a physician (gynecologist).

She decides to read, especially hepatitis B.

On her next visit she asks for an anti HDV test.

Anti HDV (+)

HDV RNA is positive.
Order anti HDV test in every HBsAg (+) pt.

Even in Sweden

AT THE VERY LEAST: Order anti HDV test if HBsAg (+), ALT high, HBV DNA low even if she/he looks very “NASHy”

ALT high, HBV DNA high, ALT continues to be high despite apparently successful NA tx
DELTA HEPATITIS - DIAGNOSIS

- Anti HDV IgM
- Anti HDV (IgG)
- HDV RNA (qualitative, quantitative PCR)
- HDV Ag (immunohistochemistry)
- Quantitative HBsAg,
- HDV & HBV genotype determination
Anti HDV IgM titre correlate with ALT and histologic activity

Wranke et al, PlosOne 2014
Effect of semi-quantitative anti HDV IgM levels on prognosis

Cumulative event free survival

IgM status
- negative
- medium
- high
- positive

Number at risk
IgM negative
- 11
- 8
- 6
- 5
- 3
- 2
IgM positive
- 67
- 48
- 37
- 27
- 19
- 13

Wranke et al, PlosOne 2014
Anti HDV IgM

- Suggestive of acute infection or chronic active infection
- Not standardized
- HDV RNA more sensitive
Anti HDV (or anti HDV IgG)

- First test to be used for searching for HDV
- Not a neutralizing Ab, depicts encounter with HDV
- HDV RNA testing necessary to establish active HDV infection
- Remains positive for years after successful tx including HBsAg clearance
HDV RNA

- Qualitative or quantitative
- Surrogate marker of tx efficacy
- Standardization was important Now there is a WHO standard (Paul Ehrlich Institute); Labs should get it
First International External Quality Assessment for Hepatitis Delta Virus RNA Quantification in Plasma

Frédéric Le Gal,¹,² Ségolène Brichler,¹–³ Roland Sahli,⁴ Sylvie Chevret,⁵,⁶ and Emmanuel Gordien¹–³

28 reference lab’s took part
13 lab’s (46%) made correct measurements
16 lab (57%) found 1-10 positive samples negative
My days at NIH

“Samples were handled with care”

“They were not dropped on the floor”
HBsAg decline in CDH

Keskin et al, Clin Gastroenterol Hepatol 2015
# HDV and HBV Genotypes

<table>
<thead>
<tr>
<th>Region</th>
<th>HDV genotype</th>
<th>HBV genotype</th>
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<tbody>
<tr>
<td>Europe</td>
<td>1</td>
<td>D / A</td>
</tr>
<tr>
<td>Brazil</td>
<td>1 / 3</td>
<td>F / A / D</td>
</tr>
<tr>
<td>China, Taiwan, Japan</td>
<td>1 / 2 / 4</td>
<td>B / C</td>
</tr>
<tr>
<td>Turkey, Romania, Albania, Iran, Pakistan, India</td>
<td>1</td>
<td>D</td>
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<td>Western Pacific</td>
<td>1 / 2</td>
<td>B / C / D</td>
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<tr>
<td>Africa</td>
<td>1, 5-8</td>
<td>D / A / E</td>
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</table>
Different HDV Genotypes Are Associated With Different Clinical Outcomes
Non-invasive fibrosis score for hepatitis delta

Gunnar L. Lutterkort¹, * | Anika Wranke¹, * | Cihan Yurdaydin² | Eva Budde³ |
Max Westphal³ | Ralf Lichtinghagen⁴ | Judith Stift⁵ | Birgit Bremer¹ |
Svenja Hardtke¹, ⁶ | Onur Keskin² | Ramazan Idilman² | Armin Koch³ |
Michael P. Manns¹, ⁶ | Hans P. Dienes⁵ | Heiner Wedemeyer¹, ⁶ | Benjamin Heidrich¹, ⁶
<table>
<thead>
<tr>
<th>Score</th>
<th>Cut-off</th>
<th>Sensitivity (% with 95%-CI)</th>
<th>Specificity (% with 95%-CI)</th>
<th>PPV (% with 95%-CI)</th>
<th>NPV (% with 95%-CI)</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST-ALT-ratio</strong>&lt;sup&gt;20,a&lt;/sup&gt; (n=100)</td>
<td>&gt;1.00 (cirrhosis)</td>
<td>18 (7–29)</td>
<td>91 (89–99)</td>
<td>62 (36–88)</td>
<td>57 (47–67)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>&gt;0.80 (new, cirrhosis)</td>
<td>47 (32–62)</td>
<td>84 (74–94)</td>
<td>70 (54–86)</td>
<td>66 (55–77)</td>
<td></td>
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<tr>
<td><strong>APRI</strong>&lt;sup&gt;21,a&lt;/sup&gt; (n=100)</td>
<td>≥1.50 (fibrosis)</td>
<td>25 (16–34)</td>
<td>70 (50–90)</td>
<td>77 (61–93)</td>
<td>19 (10–28)</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>≥0.63 (new, fibrosis)</td>
<td>83 (75–91)</td>
<td>40 (19–61)</td>
<td>85 (77–93)</td>
<td>36 (16–56)</td>
<td>0.60</td>
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<tr>
<td></td>
<td>≥2.00 (cirrhosis)</td>
<td>18 (7–29)</td>
<td>95 (89–100)</td>
<td>73 (47–99)</td>
<td>58 (48–68)</td>
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</tr>
<tr>
<td></td>
<td>≥1.85 (new, cirrhosis)</td>
<td>29 (16–42)</td>
<td>93 (86–100)</td>
<td>76 (56–96)</td>
<td>61 (51–71)</td>
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<td><strong>FIB-4 index</strong>&lt;sup&gt;22,a&lt;/sup&gt; (n=100)</td>
<td>≥1.45 (fibrosis)</td>
<td>59 (48–70)</td>
<td>55 (33–77)</td>
<td>84 (74–94)</td>
<td>25 (12–38)</td>
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<tr>
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<td>≥3.25 (fibrosis)</td>
<td>16 (8–24)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>23 (14–32)</td>
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<tr>
<td></td>
<td>≥1.94 (new, fibrosis)</td>
<td>45 (34–56)</td>
<td>85 (69–100)</td>
<td>92 (84–100)</td>
<td>28 (17–39)</td>
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<td><strong>NAFLD score</strong>&lt;sup&gt;23,b&lt;/sup&gt; (n=100)</td>
<td>&gt;0.676 (fibrosis)</td>
<td>4 (0–8)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>21 (13–29)</td>
<td>0.72</td>
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<tr>
<td></td>
<td>≥-1.855 (new, fibrosis)</td>
<td>53 (42–64)</td>
<td>90 (77–100)</td>
<td>95 (89–100)</td>
<td>32 (20–44)</td>
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<td><strong>BARD score</strong>&lt;sup&gt;24,b&lt;/sup&gt; (n=100)</td>
<td>≥2 points (fibrosis)</td>
<td>39 (28–50)</td>
<td>85 (69–100)</td>
<td>91 (81–100)</td>
<td>26 (15–37)</td>
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<tr>
<td></td>
<td>≥1 point (new, fibrosis)</td>
<td>61 (50–61)</td>
<td>75 (56–94)</td>
<td>91 (83–99)</td>
<td>33 (19–47)</td>
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<tr>
<td><strong>ELF score</strong>&lt;sup&gt;26,c&lt;/sup&gt; (n=93)</td>
<td>&gt;7.7 (fibrosis)</td>
<td>93 (87–99)</td>
<td>11 (0–26)</td>
<td>81 (73–89)</td>
<td>29 (0–62)</td>
<td>0.62</td>
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<tr>
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<td>&gt;9.8 (fibrosis)</td>
<td>39 (28–50)</td>
<td>78 (59–97)</td>
<td>88 (77–99)</td>
<td>23 (12–34)</td>
<td>0.61</td>
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<tr>
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<td>&gt;8.8 (new, fibrosis)</td>
<td>75 (65–85)</td>
<td>50 (27–73)</td>
<td>86 (78–94)</td>
<td>32 (15–49)</td>
<td></td>
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<tr>
<td></td>
<td>&gt;11.3 (cirrhosis)</td>
<td>9 (2–16)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>21 (12–30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;9.2 (new, cirrhosis)</td>
<td>62 (47–77)</td>
<td>61 (48–74)</td>
<td>57 (43–71)</td>
<td>66 (52–80)</td>
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<td><strong>SHASTA index</strong>&lt;sup&gt;27,c&lt;/sup&gt; (n=93)</td>
<td>&gt;0.39 (new, fibrosis)</td>
<td>31 (21–41)</td>
<td>89 (74–100)</td>
<td>92 (81–100)</td>
<td>24 (14–34)</td>
<td>0.49</td>
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<tr>
<td></td>
<td>&gt;1.18 (new, cirrhosis)</td>
<td>38 (23–53)</td>
<td>84 (74–94)</td>
<td>67 (48–86)</td>
<td>62 (51–73)</td>
<td>0.58</td>
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<tr>
<td><strong>PIIIINP as a solitary marker</strong>&lt;sup&gt;28,c&lt;/sup&gt; (n=93)</td>
<td>&gt;4.8 (new, fibrosis)</td>
<td>76 (66–86)</td>
<td>44 (21–67)</td>
<td>85 (76–94)</td>
<td>31 (13–49)</td>
<td>0.62</td>
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</tr>
</tbody>
</table>
TREATMENT OF CHRONIC DELTA HEPATITIS

* Evidence based successful treatment: interferon

* High dose, long treatment period (one year)

* Sustained virologic response LOW
Treatment of Hepatitis Delta With PEG-IFNα 2a: ~25% Sustained HDV RNA Clearance

**Figure 1.** Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.
PEG-IFNα 2a – Adefovir Combination Resulted in a More Pronounced HBsAg Suppression

HDV RNA Response Until Week 120
Intent-to-Treat Analysis

Patients HDV RNA negative (%)

PEG-IFNα 2a + Tenofovir
PEG-IFNα 2a + Placebo

Relapse 11/25 (44%)
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

Wedemeyer, Yurdaydin, et al. EASL 2014.
Patients with HBsAg decline >0.5 log₁₀ U/mL (%)

- PEG-IFNα 2a + Tenofovir: HBsAg loss: 4/59 patients (6.7%)
- PEG-IFNα 2a + Placebo: HBsAg loss: 3/61 patients (4.9%)

Mean HBsAg levels [log₁₀ IU/ml]

Wedemeyer, Yurdaydin, et al. EASL 2014.
No Progress in HDV Treatment, why?

• Progress in HBV tx did not contribute
  – HBV Tx acts on HBV DNA Polymerase
  – Very efficient
  – The only fn of HBV needed by HDV is HBsAg synthesis
  – NA tx in HBV has no effect on HBsAg synthesis

• RNA Polymerase is a cell enzyme and cannot be targeted for tx

• HDV is considered an ‘orphan disease’ and the potential financial reward is likely to be insufficient for the BMI to invest in CDH
Well, nobody's perfect.
HDV RNA and HBsAg kinetics in CDH during peg-IFN therapy

HDV RNA declines in a biphasic manner:
Fast 1st phase decline followed by a slow 2nd phase decline (or plateau)

HBsAg kinetics parallel kinetics of HDV RNA

There is a long delay before Peg-IFN shows an effect

Guedj J et al, Hepatology 2014
IFN treatment: Problems

• How can treatment efficacy be assessed?
• How consistent and reliable is a sustained virologic response?
• The impact of therapy in the high proportion of patients with cirrhosis
• What is the response of treatment-naïve vs treatment experienced patients?
• What is the optimal duration of treatment?
• Can response to treatment be predicted?
• Or can NRs be predicted?
• Are better markers of treatment efficacy needed?
IFN treatment: Problems

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- What is the optimal duration of treatment?
- Can response to treatment be predicted?
- Or can NRs be predicted?
- Are better markers of treatment efficacy needed?
IFN treatment: Problems

• How can treatment efficacy be assessed?
  
  Best: HBsAg clearance
  Realistic: Posttreatment HDV RNA negative

• How consistent and reliable is a sustained virologic response?
  
  Not reliable
IFN treatment: Problems

• How can treatment efficacy be assessed?
• How consistent and reliable is a sustained virologic response?
• The impact of therapy in the high proportion of patients with cirrhosis
• What is the response of treatment-naïve vs treatment experienced patients?
• What is the optimal duration of treatment?
• Can response to treatment be predicted?
• Or can NRs be predicted?
• Are better markers of treatment efficacy needed?
Figure 2A: Flow chart of maintained viral response and treatment duration

Keskin et al, AASLD 2015
Figure 2B: Cumulative probability of a maintained viral response in patients treated with interferons
Keskin et al, AASLD 2015
<table>
<thead>
<tr>
<th></th>
<th>Overall (n:99)</th>
<th>IFN responders (n:35)</th>
<th>IFN non-responders (n:64)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.0±10.6</td>
<td>41.6±9.4</td>
<td>39.2±11.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Gender</td>
<td>70 Male/29Female</td>
<td>24 Male/11 Female</td>
<td>46 M/18 F</td>
<td>0.81</td>
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<tr>
<td>HDV RNA (log_{10} IU/mL) (n:59)</td>
<td>5.98±1.4</td>
<td>6.1±1.6</td>
<td>5.9±1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>HBVDNA (log_{10} IU/mL, median (range)(n:63)</td>
<td>1.70 (1.0-7.62)</td>
<td>1.67 (1.0-4.90)</td>
<td>1.70 (1.0-7.62)</td>
<td>0.34</td>
</tr>
<tr>
<td>HBeAg status</td>
<td>81 (-) / 15 (+)</td>
<td>29 (-) / 4 (+)</td>
<td>52 (-) / 11 (+)</td>
<td>0.56</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>107±108</td>
<td>97±86</td>
<td>112±119</td>
<td>0.53</td>
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<tr>
<td>AST (U/L)</td>
<td>76±73</td>
<td>76±76</td>
<td>77±71</td>
<td>0.9</td>
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<tr>
<td>ALP (U/L)</td>
<td>115±52</td>
<td>102±52</td>
<td>123±51</td>
<td>0.07</td>
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<tr>
<td>GGT (U/L)</td>
<td>83±78</td>
<td>55±53</td>
<td>100±86</td>
<td>0.007</td>
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<tr>
<td>PT (seconds)</td>
<td>13.3±1.4</td>
<td>13.2±1.4</td>
<td>13.3±1.4</td>
<td>0.6</td>
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<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>1.01±0.5</td>
<td>0.89±0.5</td>
<td>1.08±0.6</td>
<td>0.12</td>
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<tr>
<td>Platelet (x10^{9}/L)</td>
<td>161±52</td>
<td>181±54</td>
<td>150±48</td>
<td>0.004</td>
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<tr>
<td>HAI (n:78)</td>
<td>10.9±3.9</td>
<td>10.5±4.7</td>
<td>11±3.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Cirrhosis present</td>
<td>19/99 (19%)</td>
<td>5/35 (14%)</td>
<td>14/64 (22%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Fibrosis score (n:78)</td>
<td>2.15±1.4</td>
<td>1.97±1.4</td>
<td>2.26±1.3</td>
<td>0.36</td>
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<td>HBsAg (log_{10} IU/mL, n:49)</td>
<td>3.70±0.66</td>
<td>3.40±0.79</td>
<td>3.96±0.35</td>
<td>0.004</td>
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Figure 3E

The graph illustrates the cumulative probability of liver transplantation or liver-related death over the years with and without MVR. The p-value is 0.004, indicating a statistically significant difference between the two groups.
<table>
<thead>
<tr>
<th></th>
<th>Clinical event (+)</th>
<th>Clinical event (-)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age</td>
<td>43.5±10.1</td>
<td>38.3±10.5</td>
<td>0.02</td>
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<tr>
<td>Gender</td>
<td>22 Male/10 Female</td>
<td>48 Male/19 Female</td>
<td>0.81</td>
</tr>
<tr>
<td>HBeAg status</td>
<td>28 (-) / 4 (+)</td>
<td>53 (-) / 11 (+)</td>
<td>0.67</td>
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<tr>
<td>ALT (U/L)</td>
<td>99.6±69.5</td>
<td>111.1±124</td>
<td>0.56</td>
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<tr>
<td>AST (U/L)</td>
<td>78.5±47.0</td>
<td>75.9±83</td>
<td>0.84</td>
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<tr>
<td>GGT (U/L)</td>
<td>107.7±68.8</td>
<td>71.9±81</td>
<td>0.03</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>119.0±43.7</td>
<td>114.0±56.2</td>
<td>0.65</td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>13.6±1.5</td>
<td>13.1±1.3</td>
<td>0.19</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.11±0.63</td>
<td>0.96±0.53</td>
<td>0.23</td>
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<tr>
<td>Platelet count (x10^9/L)</td>
<td>134±41</td>
<td>174±52</td>
<td>&lt;0.001</td>
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<tr>
<td>HAI Score (n:78)</td>
<td>12.5±3.3</td>
<td>10.2±4.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Fibrosis score (n:78)</td>
<td>2.68±1.35</td>
<td>1.95±1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>HDV RNA (log_{10} IU/mL) (n:59)</td>
<td>6.26±1.4 (n:18)</td>
<td>5.85±1.4 (n:41)</td>
<td>0.31</td>
</tr>
<tr>
<td>HBV DNA (log_{10} IU/mL) (n:63)</td>
<td>2.57±1.5</td>
<td>2.0±1.3</td>
<td>0.2</td>
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<tr>
<td>Cirrhosis present</td>
<td>15 (+) / 17 (-)</td>
<td>4 (+) / 63 (-)</td>
<td>&lt;0.001</td>
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<tr>
<td>IFN response</td>
<td>5 (+) / 27 (-)</td>
<td>30 (+) / 37 (-)</td>
<td>0.006</td>
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<tr>
<td>HBsAg log_{10} IU/mL, n:49</td>
<td>9239±6757</td>
<td>9252±7965</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Suppl. Figure 2A

Cirrhosis (n:19)

Chronic hepatitis (n:80)

P<0.001
Figure 4

Cumulative probability of HBsAg loss

Years

Without MVR

With MVR

p<0.001
<table>
<thead>
<tr>
<th></th>
<th>HBsAg clearance</th>
<th>No HBsAg clearance</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>Treatment duration (months)</td>
<td>29.4±21.2</td>
<td>31.8±24.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Gender</td>
<td>11 Male/3 Female</td>
<td>59 Male/26 Female</td>
<td>0.75</td>
</tr>
<tr>
<td>HBsAg (log_{10} IU/ml, n:49)</td>
<td>3.22±0.88</td>
<td>3.84±0.52</td>
<td>0.005</td>
</tr>
<tr>
<td>HBeAg status</td>
<td>11 (-)/2(+)</td>
<td>70 (-)/13(+)</td>
<td>0.90</td>
</tr>
<tr>
<td>HBV DNA (log_{10} IU/mL, n:63)</td>
<td>2.47±1.8</td>
<td>2.4±1.5</td>
<td>0.90</td>
</tr>
<tr>
<td>HDVRNA (IU/ml, n:59)</td>
<td>6.15±1.5</td>
<td>5.95±1.4</td>
<td>0.70</td>
</tr>
<tr>
<td>Age</td>
<td>39.6±6.8</td>
<td>40.1±11.1</td>
<td>0.87</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>102±54</td>
<td>108±115</td>
<td>0.86</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>86±86</td>
<td>75±71</td>
<td>0.58</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>42±26</td>
<td>91±82</td>
<td>0.03</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>115±54</td>
<td>115±52</td>
<td>0.98</td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>13.8±2.2</td>
<td>13.2±1.2</td>
<td>0.38</td>
</tr>
<tr>
<td>T.Bil (mg/dL)</td>
<td>1.06±0.8</td>
<td>1.01±0.5</td>
<td>0.75</td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td>176±62</td>
<td>158±50</td>
<td>0.32</td>
</tr>
<tr>
<td>Fibrosis Score, n:78</td>
<td>2.18±1.1</td>
<td>2.14±1.4</td>
<td>0.92</td>
</tr>
<tr>
<td>HAI Score, n:78</td>
<td>11.0±5.0</td>
<td>10.8±3.8</td>
<td>0.85</td>
</tr>
<tr>
<td>Response to IFN</td>
<td>13 responders/1 non-responder</td>
<td>22 responders/63 non-responders</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
IFN treatment: Problems

• How can treatment efficacy be assessed?
• How consistent and reliable is a sustained virologic response?
• The impact of therapy in the high proportion of patients with cirrhosis
• What is the response of treatment-naïve vs treatment experienced patients?
• What is the optimal duration of treatment?
• Can response to treatment be predicted?
• Or can NRs be predicted?
• Are better markers of treatment efficacy needed?
HDV RNA levels in INF early responders

Yurdaydin et al, J Viral Hepat 2008
**Multivariate logistic regression analysis for predicting end of treatment and post-treatment week 24 virologic response**

<table>
<thead>
<tr>
<th></th>
<th>OR 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of treatment response:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDV RNA week 24</td>
<td>1.627 1.070 – 2.474</td>
<td>0.023</td>
</tr>
<tr>
<td>Baseline HAI</td>
<td>0.586 0.366 – 0.937</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Post-treatment week 24 response:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDV RNA week 24</td>
<td>2.538 1.347 – 4.782</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Figure 2: Predictive value of on-treatment week 24 undetectable HDV RNA for post-treatment week 24 virologic response

Figure 2D: Predictive value of on-treatment week 24 HDV RNA and HBsAg levels for EOT virologic “null response” (<1 log decline of HDV RNA at EOT)

Targets in HDV Treatment

1. Attachment and viral entry
2. Uncoating and transfer to nucleus
3. Replication and export to cytoplasm
4. Virion assembly
5. Export from hepatocyte

- TLR Agonists
- Entry Inhibitors
- Nucleic Acid Polymers
- Prenylation Inhibitors
Effect of the hepatocyte entry inhibitor, Myrcludex in CDH

8 pts receive Myrcludex, 2mg/kg for 6 months
8 pts receive Myrcludex, 2mg/kg + Peg IFN for 6 months
Daily sc injections

Urban S et al, AASLD 2014, LB 20
• 6 of 7 patients experienced HDV RNA decline $>1 \log_{10}$ at week 24 during Myr B monotherapy
• 7 of 7 patients experienced HDV RNA decline $>1 \log_{10}$ at week 24 during Myr B/PEG-IFN$\alpha$ combination therapy
• HDV RNA became negative in 2 patients during MyrB monotherapy and in 5 patients in combination with PEG-IFN$\alpha$
Heparin sulfate glycoproteins as HBV-HDV rec’s's

Treatment of CDH with Lonafarnib

Mean (SD) Change in HDV RNA Per Week

- Placebo
- Lonafarnib 100mg BID
- Lonafarnib 200mg BID

Koh C et al, Lancet Infect Dis 2015
Week 4 Reduction in HDV RNA with Lonafarnib

**National Institutes of Health**
NIH POC (Lancet Infect. Dis. 2015)

- Placebo
- Lonafarnib 100 mg BID
- Lonafarnib 200 mg BID

**Ankara University**
LOWR-1 (EASL 2015)

- Lonafarnib 100 mg BID
- Lonafarnib 100 mg TID
- Lonafarnib 200 mg BID
- Lonafarnib 300 mg BID
- Lonafarnib 100 mg BID + Ritonavir 100 mg QD
- Lonafarnib 100 mg BID + PEG IFN-α 2a 180 mcg QW

Mean ∆:
- 0.5
- 0
- 0.2 Log
- 0.74 Log
- 1.2 Log
- 1.6 Log
- 1.8 Log
- 2.0 Log
- 2.4 Log

N:
- 4
- 6
- 6
- 3
- 3
- 3
- 3
- 3
Side effects
Lonafarnib With Ritonavir in HDV

- Mainly GI side effects

<table>
<thead>
<tr>
<th>Grade</th>
<th>N=3 LNF 200 mg BID</th>
<th>N=3 LNF 300 mg BID</th>
<th>N=3 LNF 100 mg BID RTN 100 mg QD</th>
<th>N=3 LNF 100 mg BID PEG IFN 180 mcg QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Wt Loss</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

- Observed in almost every patient
- Lonafarnib chronically dosed for 2 years in a pediatric population (Progeria - PNAS, 2012, 16666)
Serum Concentration and Viral Load
Statistically Significant Linear Relationship

Fig. 4 Inhibiting lonafarnib’s metabolism with ritonavir increases antiviral response
Effect of ARC-520, a siRNA based tx as single injection on HBsAg levels in HBeAg (-) CHB

Yuen MF et al, AASLD 2014, LB 21
Nucleic acid polymers (NAPs) are oligonucleotides whose biochemical function is strictly dependent on the polymer chemistry of oligonucleotides.

They bind with high affinity to amphipathic protein structures.

These amphipathic protein structures are very rare in normal human biology (already complexed with each other inside proteins where they help stabilize the protein structure).

However amphipathic targets are required for various stages of viral replication. NAPs effectively block the functions of these proteins, providing an effective, broad-spectrum antiviral activity.
Nucleic Acid Polymers (NAPS) for HBV/HDV Coinfection

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

Results: (1) HBsAg

Results: (2) HDV RNA

Vaillant A, et al. EASL 2015, Vienna. #LO2
Summary and Conclusion- 1

The only effective treatment is with interferons

Treatment beyond 1 year needed in a sizeable proportion of patients

Post-treatment week 24 ≠ SVR in CDH

HDV RNA standard now available
Summary and Conclusion- 2

The future:
There is now hope:
Hepatocyte entry inhibitors
Prenylation inhibitors
Nucleic acid polymers
siRNAs

Stay tuned