Prolonged therapy of hepatitis delta for 96 weeks with PEG-IFNa-2a plus tenofovir or placebo does not prevent HDV RNA relapse: The HIDIT-2 study.


for the HIDIT-2 Study Group

* Cihan Yurdaydın and Heiner Wedemeyer contributed equally
Disclosure

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- Roche Turkey
- Roche -Basel, Roche-Germany, Roche-Romania & Roche-Greece
- Gilead Sciences

H. Wedemeyer discloses that he has received
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The HIDIT-2 Study Group:


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Hannover Clinical Trial Center:

Biostatistics + Data analysis
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Hepatitis Delta

- Hepatitis delta is the most severe form of chronic viral hepatitis
- Approximately 15-20 million individuals worldwide are anti-HDV positive

Rizzetto et al., J of Hepatology 2009
Yurdaydın J Viral Hepatitis 2010
Wedemeyer & Manns Nat Rev Gastroenterol 2010
Hughes et al., Lancet 2011

www.hepatitis-delta.org
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, Yurdaydin et al. NEJM 2011

HDV RNA negative [%]

Patients (%) HDV-RNA negative [%]

- Peginterferon alfa-2a + adefovir
- Peginterferon alfa-2a + placebo
- Adefovir

AHDV-RNA

Median HBsAg

Week 48, End of Treatment

Week 72, End of Follow-up

Median HBsAg (log_{10} IU/ml)

Baseline 24 48 72 Week

Wedemeyer, Yurdaydin et al. NEJM 2011
However: Late relapses may occur!

*Heidrich et al., Hepatology 2014:*

5 years long-term follow-up

- 9/16 patients classified initially as post-treatment week 24 responder tested HDV RNA positive during further follow up
Treatment of hepatitis delta with pegylated interferon alfa

Can prolonged treatment improve response rates and prevent post-treatment relapse?

Is there a role for combination with tenofovir?
The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2

96 weeks

PEG-Interferon alpha-2a 180µg oiw + Placebo

5 years FU

N=61

Follow-up

Stratification:
Country
Previous therapy
Gender

N=59

PEG-Interferon alpha-2a  180µg oiw + Tenofovir disoproxilfumarat 245mg daily

Follow-up

Primary efficacy endpoint: HDV RNA negativity Week 96

This presentation: Post-Treatment week 24 results
The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2

- 2 parallel trials with an identical protocol but combined analysis
- Sponsor German Hep-Net:
  Germany (n=46), Romania (n=19), Greece (n=5)
- Sponsor Roche Turkey
  Turkey (n=50)
- Central Virological laboratory for both trials
  Hannover Medical School
  HDV RNA assays: Mederacke et al., J Clin Microbiol 2010
- Analysis by intention to treat

Predefined efficacy endpoints:
- HDV RNA negativity, HBsAg loss, HBsAg decline >0.5 log IU/ml
- ALT normalization.
Inclusion criteria

• Adults with chronic delta hepatitis
• Compensated liver disease
• HBsAg positive for at least 6 months
• anti HDV positive for at least 3 months
• HDV RNA positive by PCR
• ALT $\geq$ ULN to $\leq$10x ULN
• Negative tests for HCV-RNA & anti-HIV
• No treatment for hepatitis D in the prior 6 months
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN a Tenofovir (n=59)</th>
<th>PEG-IFNa Placebo (n=61)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [ mean years]</strong></td>
<td>38</td>
<td>42</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Sex [female/male]</strong></td>
<td>21/38</td>
<td>20/41</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>cirrhosis at screening</strong></td>
<td>24 (41%)</td>
<td>25 (41%)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Previous IFN-Therapy</strong></td>
<td>29 (49%)</td>
<td>31 (51%)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>ALT [mean IU/l]</strong></td>
<td>110</td>
<td>122</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Patients with ALT &gt;5xULN</strong></td>
<td>7 (12%)</td>
<td>4 (6.8%)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>HBeAg positive</strong></td>
<td>12 (20%)</td>
<td>8 (13%)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>HDV RNA [median log10 cop/ml]</strong></td>
<td>5.26</td>
<td>5.18</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>HBV DNA [median log10 IU/ml]</strong></td>
<td>2.65</td>
<td>2.70</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>HBsAg [median log10 IU/ml]</strong></td>
<td>3.94</td>
<td>3.91</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Safety

• 20 patients did not complete at least 80 weeks of therapy
  11 placebo / 9 tenofovir

• 976 adverse events (every patient had at least 1 AE)
  515 AEs in placebo-treated patients
  461 AEs in tenofovir-treated patients

• 65 serious adverse events in 39 patients
  30 SAEs in placebo-treated patients (31% of patients); 22 (73%) unrelated
  35 SAEs tenofovir-treated patients (34% of patients); 24 (69%) unrelated

• 2 Deaths: 1 in each study arm (Possibly related to PEG-IFNa)
  one mitral valve rupture
  One death pneumonia/sepsis 6 months after therapy
HDV RNA response (Intent-to-treat analysis)

% of patients HDV RNA negative

- Baseline
- W12
- W24
- W48
- Week 96

PEG-IFNa-2a + Tenofovir
PEG-IFNa-2a + Placebo

Per-Protocol Analysis (n=99)

Week 96

- PEG-IFNa-2a + Tenofovir: 54%
- PEG-IFNa-2a + Placebo: 41%

p=0.10
p=0.19
HDV RNA response until week 120 (Intent-to-treat analysis)

% of patients HDV RNA negative

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>W12</td>
<td></td>
<td></td>
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<tr>
<td>W24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W48</td>
<td></td>
<td></td>
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<tr>
<td>Week 96</td>
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</tr>
</tbody>
</table>

PEG-IFNa-2a + Tenofovir
PEG-IFNa-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

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

Baseline W12 W24 W48 Week 96

p=0.10

47% 33%

p=0.34

30% 23%

week 120 24 w post Tx

weeks 120

HU

24 w post Tx

Wedemeyer, Yurdaydin et al. EASL–ILC 2014
The HIDIT-2 Study
HDV RNA levels until week 120

Mean HDV RNA levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean HDV RNA levels [copies/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFNa-2a + Tenofovir</td>
<td></td>
</tr>
<tr>
<td>PEG-IFNa-2a + Placebo</td>
<td></td>
</tr>
</tbody>
</table>

- Baseline
- Week 12
- Week 24
- Week 48
- Week 72
- Week 96
- Week 120
HBsAg response until week 120 (Intent-to-treat analysis)

% of patients with HBsAg-decline >0.5 Log10IU/ml

HBsAg loss: 4/59 patients (6.7%)
HBsAg loss: 3/61 patients (4.9%)

PEG-IFNa-2a + Tenofovir
PEG-IFNa-2a + Placebo

Mean HBsAg levels [log10 IU/ml]
ALT response until week 96 (Intent-to-treat analysis)

- **PEG-IFNa-2a + Tenofovir**
- **PEG-IFNa-2a + Placebo**

% of patients with normal ALT values

Mean ALT Values

Wedemeyer, Yurdaydin et al. EASL–ILC 2014
The HIDIT-2 Study
Factors associated with HDV RNA negativity at Week 120

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95%-Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Arm</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo vs. Tenofovir</td>
<td>0.961</td>
<td>0.441</td>
<td>2.085</td>
</tr>
<tr>
<td>Age [years]</td>
<td>1.004</td>
<td>0.971</td>
<td>1.039</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>1.601</td>
<td>0.706</td>
<td>3.627</td>
</tr>
<tr>
<td>Cirrhosis at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs. Yes</td>
<td>0.290</td>
<td>0.128</td>
<td>0.656</td>
</tr>
<tr>
<td>ALT [log U/L]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 0.5 log IU/ml</td>
<td>0.159</td>
<td>0.086</td>
<td>0.314</td>
</tr>
<tr>
<td>platelets [10³µl]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5<em>ULN &amp; ≤5</em>ULN vs. &gt;5*ULN</td>
<td>1.159</td>
<td>0.648</td>
<td>2.032</td>
</tr>
<tr>
<td>HBV-DNA at baseline</td>
<td></td>
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<tr>
<td>≥150 vs. &lt;150</td>
<td>1.134</td>
<td>0.459</td>
<td>2.953</td>
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<tr>
<td>HDV-RNA at baseline</td>
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<tr>
<td>≥150 vs. &lt;150</td>
<td>0.331</td>
<td>0.128</td>
<td>1.014</td>
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<tr>
<td>HBsAG at baseline</td>
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<tr>
<td>≥0.5 log IU/ml</td>
<td>3.442</td>
<td>1.442</td>
<td>8.217</td>
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<tr>
<td>HBsAG decline until week 96</td>
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<tr>
<td>≥0.5 log IU/ml</td>
<td>3.442</td>
<td>1.442</td>
<td>8.217</td>
</tr>
<tr>
<td>Country</td>
<td></td>
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<tr>
<td>Germany vs. Turkey</td>
<td>1.196</td>
<td>0.496</td>
<td>2.885</td>
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<td>Greece vs. Turkey</td>
<td>0.739</td>
<td>0.062</td>
<td>8.868</td>
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<td>Romania vs. Turkey</td>
<td>1.457</td>
<td>0.489</td>
<td>4.341</td>
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<td>Previous Interferon-Therapy</td>
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<tr>
<td>yes vs. No</td>
<td>0.914</td>
<td>0.419</td>
<td>1.992</td>
</tr>
</tbody>
</table>

Week 120 HDV RNA Response:
Patients Cirrhosis: 51% vs. Non-cirrhotic patients: 25%
Summary

• 96 weeks of PEG-IFNa-2a and tenofovir therapy is possible but associated with a high frequency of SAEs

• Combination treatment showed numerically higher rates of on-treatment HDV RNA suppression but similar effects on HBsAg reduction as compared to PEG-IFNa-2a alone

• Liver cirrhosis is associated with higher response rates

• HBsAg levels are predictive of HDV RNA response

• More than one third of patients experience a post-treatment HDV RNA relapse despite prolonged therapy
Conclusions

- Patients with hepatitis delta and compensated liver cirrhosis should be treated with PEG-IFNa.
- Combination therapy with tenofovir does not provide obvious benefits in hepatitis delta patients with low baseline HBV-DNA levels.
- 96 weeks of PEG-IFNa treatment does not provide higher off-treatment HDV RNA responses (compared to 48 weeks in the HIDIT-1 study).
- HBsAg levels may be used to individualize treatment duration.
- Alternative treatment options are urgently needed for HDV-infected patients.