Hepatitis Delta Revival

Heiner Wedemeyer

Medizinische Hochschule Hannover
## HEPATITIS VIRUSES

<table>
<thead>
<tr>
<th>Hepatitis Type</th>
<th>Name</th>
<th>Year</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Feinstone</td>
<td>1973</td>
<td>RNA</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Blumberg</td>
<td>1965</td>
<td>DNA</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Houghton</td>
<td>1988</td>
<td>RNA</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Rizzetto</td>
<td>1977</td>
<td>RNA</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Balayan</td>
<td>1980</td>
<td>RNA</td>
</tr>
</tbody>
</table>
EASL Monotheematic Conference: Delta Hepatitis
September 24-26, 2010
Istanbul, Turkey
M Manns, M Rizzetto, C Yurdaydin
Declining Prevalence of Hepatitis D Virus Infection in Italy

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Gaeta, Rizzetto et al., Hepatology 2000
HDV-Infection in Germany

Anti-HDV-Prevalence in HBsAg+ patients
Hannover Medical School
(1-1992 bis 4-2006; n=2354)

% anti HDV+ / HBsAg+


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Wedemeyer et al., Hepatology 2007
HDV-Infection in Germany

Anti-HDV-Prevalence in HBsAg+ patients
Hannover Medical School
(1-1992 bis 4-2006; n=2354)

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Wedemeyer et al., Hepatology 2007
Emerging HDV Epidemiology: Migration

HDV Prevalence
- High
- Intermediate
- Low
- Very Low
- No Data

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Long-term outcome of hepatitis D in Italy

A. Developing cirrhosis

B. Clinical Decompensation

C. Hepatocellular Carcinoma

Main Cause of Death: Liver Failure (38%)

Only independent Factor of mortality: HDV replication
Hepatic Decompensation but not HCC development is the primary cause of mortality.
Diagnostic Steps in Delta Hepatitis

HBsAg+ → Anti-HDV+

HDV-RNA-neg

HDV-RNA-pos → HDV-RNA quantitative
Quantitative HDV-PCR: Cobas-TaqMan Assay

R²=1.000

R²=0.9203

R²=0.9993

R²=0.9963

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Mederacke et al. J Clin Microbiol 2010
Diagnostic Steps in Delta Hepatitis

\[ \text{HBsAg}^+ \rightarrow \text{Anti-HDV}^+ \]

- HDV-RNA-neg
- HDV-RNA-pos
- HDV-RNA quantitative

Does HDV viremia correlate with the stage/grade of liver disease?
HDV-RNA does **NOT** correlate with liver fibrosis

<table>
<thead>
<tr>
<th></th>
<th>HDV-RNA&lt; $10^5$ copies/ml (n=20)</th>
<th>HDV-RNA&gt; $10^5$ copies/ml (n=47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ishak fibrosis score</strong></td>
<td>3.4 ± 0.9</td>
<td>3.2 ± 1.4</td>
<td>NS*</td>
</tr>
<tr>
<td><strong>Cirrhosis (Ishak 5-6) (%)</strong></td>
<td>2 (10)</td>
<td>11 (23.4)</td>
<td>NS $$$</td>
</tr>
<tr>
<td><strong>Significant fibrosis (Ishak 3-6) (%)</strong></td>
<td>16 (80)</td>
<td>31 (66)</td>
<td>NS $ $</td>
</tr>
</tbody>
</table>
Diagnostic Steps in Delta Hepatitis

- HBsAg+ → Anti-HDV+
  - HDV-RNA-neg → Repeat PCR
    - ALT levels, Histology?
  - HDV-RNA-pos
    - HDV-RNA quantitative
    - HDV Genotype

Does the course of Delta Hepatitis differ between different genotypes?
Different HDV genotypes in different regions

HDV prevalence
- High
- Intermediate
- Low
- Very low
- No data

Wedemeyer et al., Nat Rev Gastroenterol 2010
Different HDV genotypes are associated with different clinical outcomes

Su et al, Gastroenterology 2006
Diagnostic Steps in Delta Hepatitis

- HBsAg+
- Anti-HDV+
- HDV-RNA-neg → Repeat PCR ALT levels, Histology?
- HDV-RNA-pos
  - HDV-RNA quantitative
  - HDV Genotype
- HBeAg
- HBV-DNA
HBeAg and HBV-DNA are suppressed in Delta Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>aHDV positive</th>
<th>HBsAg+ / aHDV negative</th>
<th>$\chi^2$ p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg positive</td>
<td>44/ 257 (17%)</td>
<td>610/ 2024 (30%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBV-DNA positive</td>
<td>59/ 228 (25%)</td>
<td>708/ 1562 (45%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Heidrich et al, J Viral Hepatitis 2009
HDV p24 & p27 repress HBV enhancers

HBsAg (Cytoplasm)

O.D/β-Galactosidase

Fold induction

Williams, Gordien et al, J General Virology 2009
Diagnostic Steps in Delta Hepatitis

Fluctuating Patterns of Viral Dominance maybe observed over time

- HBsAg+
- Anti-HDV+
- HDV-RNA-neg
  - Repeat PCR
  - ALT levels, Histology?
- HDV-RNA-pos
- HDV-RNA quantitative
- HDV Genotype

- HBeAg
- HBV-DNA

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Fluctuating Patterns of Viral Dominance in Hepatitis D

Fig. 1. Schematic representation of HBV DNA and HDV RNA patterns over time observed in the study by Schaper et al. [19].
Treatment of Delta Hepatitis?
## HDV-Infection Treatment Options

### Nucleos(t)ide Analogues

- Famciclovir ineffective
  - Yurdaydin et al., J Hepatol 2002
- Lamivudine ineffective
  - Wolters et al., J Viral Hepatitis 2000
  - Niro, Aliment Pharmacol Ther. 2005; Niro et al., J Viral Hepatitis 2008
  - Yurdaydin et al., J Viral Hepatitis 2008
- Ribavirin ineffective
  - Niro et al., Hepatology 2006
  - Garripoli et al., Liver 1994
  - Gunsar et al., Antiv Therapy 2005

### Interferon alpha

- Sustained biochemical responses in 0-36% of patients
  - Few Studies with virological endpoints
  - treatment >12 months may be required
  - Farci et al., NEJM 1994
  - Di Marco et al., J Viral Hepatitis 1996
  - Niro et al., J Viral Hepatitis 2005; Yurdaydin et al., J Viral Hepatitis 2008
- Higher IFN doses were associated with better survival in small study cohort
  - Farci et al., Gastroenterology 2004
Farci et al., IFNa for HDV infection (NEJM 1994 / Gastroenterology 2004)

Proportion of Patients Surviving

Years After Termination of Therapy

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Trials using PEG-IFN in Delta Hepatitis
3 studies published in September 2006

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Journal</th>
<th>Patients, Duration</th>
<th>Treatment</th>
<th>SVR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelnau, Marcellin, Gault et al.</td>
<td>Hepatology 2006</td>
<td>14 patients, 12 months of PEG-IFNα-2b</td>
<td>SVR in 6 patients (43%)</td>
<td></td>
</tr>
<tr>
<td>Niro, Rizzetto et al.</td>
<td>Hepatology 2006</td>
<td>38 patients, 72 weeks PEG-IFNα-2b</td>
<td>16 pts monotherapy</td>
<td>SVR: 8 patients (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22 pts + ribavirin (first 48 weeks)</td>
<td>Ribavirin had no additional effect</td>
</tr>
<tr>
<td>Erhardt, Häussinger et al.</td>
<td>Liver Int 2006</td>
<td>12 patients, 48 weeks of PEG-IFNα-2b</td>
<td>SVR in 2 patients (17%)</td>
<td></td>
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</tbody>
</table>
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.
Combination Therapy shows more pronounced HBsAg decline!

**B HBsAg Levels over Time**

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

Median HBsAg (log₁₀ IU/ml)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24</th>
<th>48</th>
<th>72</th>
</tr>
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<tbody>
<tr>
<td>Peginterferon alfa-2a + placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adefovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon alfa-2a + adefovir</td>
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**Week**

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Wedemeyer, Yurdaydin et al. NEJM 2011
Alternative Treatment options?
Liver Transplantation for Hepatitis D?
Collaborators:

C. Yurdaydin; Turkey
G. Dalekos + G. Papatheodoridis Greece
J.M. Pawlotski + E. Gordien; France
The HIDIT STUDY GROUP

Michael P. Manns
Markus Cornberg
Beatrice Calle-Serrano, Benjamin Heidrich
Jan Grabowski, Ingmar Mederacke, Kalliopi Zachou
Kerstin Port, Birgit Bremer, Janina Kirschner
Become an EASL Member!