Update on Treatment on Treatment of Hepatitis B and C

Heiner Wedemeyer

Medizinische Hochschule Hannover
H. Wedemeyer – 3-2010:
Update on Treatment of Hepatitis B and C
HCV ≠ HBV
The HCV life cycle: Cure is possible!
The HBV-Lifecycle: No cure unless the infected cell is deleted!

- Virion
- Uncoating
- Partially double-stranded DNA
- (+) DNA
- (-) DNA
- cccDNA
- mRNA
- Pre-genomic RNA
- HBsAg envelope
Hepatitis B
EASL Clinical Practice Guidelines: Management of chronic hepatitis B
European Association for the Study of the Liver*

www.easl.eu
Goals of treatment?
HBs-Seroconversion

HBe-Seroconversion

HBV-DNA Suppression
Hepatitis B Treatment: Different concepts

(PEG)-INTERFERON ALPHA

- HBs-Seroconversion up to 10%
- HBe-Seroconversion up to 50% in certain subgroups (Genotype A)
- No natural resistance
- Finite therapy (48 weeks)

- Side effects, contraindications limit the use of IFN

Nucleos(t)id-Analogues

- High antiviral activity
- Few side effects
- Can be used in patients with decompensated cirrhosis

- Drug resistance becomes challenge
- High relapse after discontinuation of treatment
- Long-term treatment (years…)

H. Wedemeyer – 3-2010: Update on Treatment of Hepatitis B and C
When to use IFNa for hepatitis B?
(PEG-) IFNa to treat chronic hepatitis B

• High ALT
• Low HBV-DNA
• Genotype A
PEG-IFNα -2b +/- Lamivudine: HBeAg-loss by genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Patients (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>47%</td>
<td>90</td>
</tr>
<tr>
<td>B</td>
<td>44%</td>
<td>23</td>
</tr>
<tr>
<td>C</td>
<td>28%</td>
<td>39</td>
</tr>
<tr>
<td>D</td>
<td>25%</td>
<td>103</td>
</tr>
</tbody>
</table>

Janssen et al, Lancet 2005
HBV-genotype A: Distribution in Europe

Deterding et al., J Med Virol 2008
How to use HBV polymerase inhibitors?

Nucleos(t)ides

Patients with liver cirrhosis

nucleos(t)die analogue with high resistance barrier or combination therapy
How to use HBV polymerase inhibitors?

**Nucleos(t)ides**

- **No liver cirrhosis**
  - Every approved nucleos(t)die analogue choice according to: virus load, comorbidity, etc.

- **Patients with liver cirrhosis**
  - Nucleos(t)die analogue with high resistance barrier or combination therapy.
Can liver fibrosis regress?
Effect on clinical endpoints?
Improvement of liver fibrosis during long-term ETV treatment

Stage 6
Baseline

Stage 6
Week 48

Stage 2
Week 268
Entecavir vs. Adefovir in patients with decompensated hepatitis B

Randomization 1:1

Baseline

Week 24

Week 48

Week 96

Open-label

ETV 1.0 mg, once daily

ADV 10 mg, once daily

Long-term Observation

Year 5

Liaw Y-F, et al., AASLD 2009; Poster # 422.
ETV vs. ADV in decomp. Hepatitis B
Overall Survival

Liaw Y-F, et al., AASLD 2009; Poster # 422.
How to use HBV polymerase inhibitors?

- **Nucleos(t)ides**

  - **no liver cirrhosis**
    - every approved nucleos(t)ide analogue choice according to: virus load, comorbidity, etc.

  - **Patients with liver cirrhosis**
    - nucleos(t)ide analogue with high resistance barrier or combination therapy

**Ideal:** high genetic barrier and strong antiviral efficacy
**Antiviral efficacy**

* no “head-to-head” studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HBeAg(+)</th>
<th>HBeAg(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>76</td>
<td>94</td>
</tr>
<tr>
<td>Entecavir</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>Telbivudine*</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>Lamivudine*</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>Peg IFN#</td>
<td>25</td>
<td>63</td>
</tr>
<tr>
<td>Adefovir§</td>
<td>21</td>
<td>51</td>
</tr>
</tbody>
</table>

*Undetectable <300 copies/mL
#Undetectable <400 copies/mL
§Undetectable <1000 copies/mL

Marcellin et al., AASLD 2007, Heathcote et al., AASLD 2007

Resistance

- Tenofovir after 3 years: 0%
- Entecavir after 6 years: <2%
- Lamivudine: 71%
- Telbivudine: 18%
- Adefovir: 29%

HBV: Overlapping reading frames!
Resistant Variants may escape vaccination

„Conclusion: .... our data showing successful experimental infection by HBV mutants despite the presence of high anti-HBs levels considered protective in the vaccinated host ....“

Hepatitis D (Delta)
Hepatitis Delta:
15-20 Million individuals world-wide!
**Long-term outcome of hepatitis D in Italy**

**Developing cirrhosis**

**Clinical Decompensation**

**Hepatocellular Carcinoma**

*Main Cause of Death:*
*Liver Failure (38%)*

*Only independent Factor of mortality:*
*HDV replication*
The Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT-1)

PEG-IFNa-2a (180 µg oiw)
Adefovir dipivoxil 10 mg daily

PEG-IFNa-2a (180 µg oiw)
Placebo

Adefovir dipivoxil 10 mg daily

N=32*

N=91

N=30

N=29

Screening

TW0

TW24

TW48

F24
PEG-IFN leads to sustained suppression of HDV-RNA in about 25% of patients.
Hepatitis C
>50% cure of chronic Hepatitis C

Sustained virological response

- IFN & Ribavirin 48 weeks
- PEG-IFN 48 weeks
  - 12 kDa PEG-IFN alfa-2b
  - 40 kDa PEG-IFN alfa-2a

Definitions of Response Kinetiks

- **RVR**
- **cEVR/EVR**
- **Slow responder**

Cornberg, Deterding, Manns. Expert Reviews of Anti-infective Therapy 2006
H. Wedemeyer – 3-2010:
Update on Treatment of Hepatitis B and C

**Therapiebeginn**
(HCV RNA Konzentration)

**Woche 4**
HCV RNA Bestimmung

**Woche 12**
HCV RNA Bestimmung

**Woche 24**
HCV RNA Bestimmung

24 Wochen Therapie
*Rapid-Responder*
RVR

48 Wochen Therapie
*Standard-Responder*
cEVR

72 Wochen Therapie
*Slow-Responder*

Therapieabbruch

HCV RNA <12-15 IU/ml
1

HCV RNA <12-15 IU/ml
2

HCV RNA mit einem hochsensitiven Assay nicht nachweisbar, <12-15 IU/ml oder <50 IU/ml je nach verwendetem Assay.

Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance

Dongliang Ge¹, Jacques Fellay¹, Alexander J. Thompson², Jason S. Simon³, Kevin V. Shianna¹, Thomas J. Urban¹, Erin L. Heinzen¹, Ping Qiu³, Arthur H. Bertelsen¹, Andrew J. Muir², Mark Sulkowski¹, John G. McHutchison² & David B. Goldstein¹

Genome-wide association of IL28B with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

Genetics

IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy

Vijayaprakash Suppiah¹,², Max Moldovan¹, Golo Ahlenstiel³, Thomas Berg³, Martin Weltman³, Maria Lorena Abate⁴, Margaret Bassendine⁵, Ulrich Spengler⁴, Gregory I Dore⁶,⁹,¹⁰, Elizabeth Powell¹¹,¹², Stephen Riordan¹³, David Sheridan⁴, Antonina Smedile⁴, Vincenzo Fragomeli⁴, Tobias Müller⁵, Melanie Bahlo³, Graeme J Stewart², David R Booth⁷ & Jacob George¹, for the Hepatitis C Study¹⁴.
IL28B Genotype and Response to PEG-IFNa + Ribavirin Therapy

Figure 1 | Percentage of SVR by genotypes of rs12979860. Data are percentages ± s.e.m.
Nonresponder Patients
Prolonged Therapy of Advanced Chronic Hepatitis C with Low-Dose Peginterferon

H. Wedemeyer – 3-2010: Update on Treatment of Hepatitis B and C
Di Bisceglie et al., NEJM Dec 2008
Future Treatment of Hepatitis C
Clinical Development of New Anti-HCV Drugs

Thompson, McHutchison et al., J Hepatol 2009
Treatment Targets against HCV

- Receptor binding and endocytosis
- Fusion and uncoating
- (+) RNA
- Transport and release
- Virion assembly
- RNA replication
- Translation and polyprotein processing

**Protease Inhibitors**

**Polymerase Inhibitors**
Telaprevir
“Prove-2-Study”

Week 12
Placebo + PegIFN alfa-2a 180 µg/week + RBV 1000-1200 mg/day (n = 82)

TVR + PegIFN alfa-2a + RBV (n = 81)

TVR + PegIFN alfa-2a + RBV (n = 82)

TVR + PegIFN alfa-2a (n = 78)

Week 24
Week 36
Week 48
Week 72
Follow-up

SVR
46%
69%
60%
36%

Telaprevir:
RVR ~70%, SVR ↑~20-25%

Hezode et al., NEJM 2009
H. Wedemeyer – 3-2010:
Update on Treatment of Hepatitis B and C
Treatment of Viral Hepatitis

The Vision

1 Tablet Cure

Vaccine / Immunotherapy?
Possible scenarios for the treatment of HCV infection in the 2020ies

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>PI</th>
<th>Pol Inh I</th>
<th>Pol Inh II / Other Antiviral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>PI</th>
<th>Pol Inh I</th>
<th>Pol Inh II / Othe antiviral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEG-IFN</th>
<th>PI</th>
<th>Pol Inh I</th>
<th>Pol Inh II</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pol Inh I</td>
</tr>
<tr>
<td>Pol Inh II</td>
</tr>
<tr>
<td>Antiviral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pol Inh I</td>
</tr>
</tbody>
</table>

H. Wedemeyer – 3-2010:
Update on Treatment of Hepatitis B and C
Possible scenarios for the treatment of HCV infection in the 2020ies
Become an EASL Member!