New Aspects of Treatment of Hepatitis C

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New Aspects of Treatment of HCV

• Aim of antiviral therapy
  – Sustained eradication of HCV

• Interferon-based antiviral treatment
  – Improvement of sustained virologic response?
  – Individualized treatment?

• New antiviral drugs
  – target, duration, combination, resistance?
  – Improvement of sustained Response?
New Aspects of Treatment of HCV

• Is cure of HCV possible?

Peg alfa-2a Mono
Peg alfa-2a + RBV elevated ALT
Peg alfa-2a + RBV normal ALT
Peg alfa-2a Mono Peg alfa-2a + RBV HCV/HIV co-infection

long-term Follow-up
mean 4.1 years (range 0.4-7) (n=997)

long-term Sustained response 989/997 patients (>99%)

Relapse 8/997 patients after mean 2 years (range 1.1-2.9 years)

Swain MG et al 2007;46:3.
Individualisation of treatment

- **NR** ($c < 0.2$): No response
- **FPR** ($0.0 \leq \delta < 0.05$): Early partial response
- **RVR** ($\delta \geq 0.35$): Early complete response
- **SPR** ($0.05 \leq \delta < 0.35$): Sustained partial response

Serum HCV RNA (log) vs. Days

**Limit of detection**

Shorter treatment duration without compromising response

Improvement of response

→ Longer treatment duration?
The "2 log₁₀ decline"

<table>
<thead>
<tr>
<th>decline of HCV-RNA at week 12</th>
<th>Non Responder</th>
<th>Sustained virologic Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 log₁₀</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>≥2 log₁₀</td>
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</table>

Does longer treatment duration (72 weeks) improve sustained virologic response?
Genotype 1: Extended Treatment

Berg, et al. Gastroenterology 2006;130:1086-1097
Genotype 1: Extended Treatment

HCV-RNA positive at week 4

- **HCV-1**
  - 48 wks: 28% (P=0.003)
  - 72 wks: 44%

- **HCV-1 / <800,000 IU/mL**
  - 48 wks: 27% (P=0.002)
  - 72 wks: 51%

- **HCV-1 / >800,000 IU/mL**
  - 48 wks: 28%
  - 72 wks: 37% (P=0.35)

Sanchez-Tapias et al., *Gastroenterology* 2006;131:451-460
Interferon based treatment

Genotype 1

- low baseline viral load
- <2 log_{10} Decline
- NPV 48 Wks 92-96%
- NPV 72 Wks 85-88%

non-response at week 4

non-response at week 12

response at week 24

Extended treatment duration of 72 weeks

<6000 IU/ml
Genotype 1: Shorter Treatment

**Shorter Treatment (24 weeks) without compromising sustained virologic response?**
Genotype 1: Shorter Treatment

Patients with HCV 1 and baseline HCV-RNA <600,000 IU/ml (n=235)

- SVR: 89% at Week 4 (47%)
- Relapse: 8% at Week 4 (47%)
- SVR: 75% at Week 12 (26%)
- Relapse: 25% at Week 12 (26%)
- SVR: 80% at Week 24/EOT (10%)
- Relapse: 17% at Week 24/EOT (10%)

Time to virologic response
PEG-IFN α-2b + RBV for 24 weeks

Zeuzem et al., J Hepatol 2006

Historical control: SVR 71%, Manns et al. Lancet 2001
Summary

Interferon based treatment

- Genotype 1
  - low baseline viral load
    - response at week 4
      - 24 weeks of antiviral treatment without compromising SVR
    - non-response at week 4
      - 24 weeks of antiviral treatment without compromising SVR
    - non-response at week 12
      - response at week 24
        - Extended treatment duration of 72 weeks
Genotype 2, 3: Shorter Treatment

*Shorter Treatment (less 24 weeks) without compromising sustained virologic response?*
Genotype 2, 3: Shorter Treatment

Shiffman et al., Late-Breaker Abstract EASL 2006

Sustained virologic response [%]

- **All**: 65% (679) vs. 76% (630), p<0.001
- **GT 2**: 65% vs. 82%, p<0.001
- **GT 3**: 65% vs. 71%

Shiffman et al., Late-Breaker Abstract EASL 2006
Genotype 2, 3: Shorter Treatment

Shorter Treatment duration without compromising sustained virologic response

- **82%** for Group A (16 weeks, HCV-RNA <600 IU/ml at week 4)
- **81%** for Group B (24 weeks, HCV-RNA <600 IU/ml at week 4)
- **39%** for Group C (24 weeks, HCV-RNA ≥600 IU/ml at week 4)

SVR B vs C: P = 0.003

v. Wagner et al, *Gastroenterology* 2005
M-L Yu et al, *GUT* 2006 (SVR Genotyp 2 16 vs. 24 Wochen: 94% vs. 95%)
Genotype 2, 3: Shorter Treatment

Th: PEG-IFN alfa-2b 1.0 µg/kg + RBV 1000-1200 mg

<table>
<thead>
<tr>
<th>Group</th>
<th>SVR (%)</th>
<th>Treatment Duration</th>
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<tbody>
<tr>
<td>Group A</td>
<td>76%</td>
<td>Standard (24 weeks)</td>
</tr>
<tr>
<td>Group A</td>
<td>76%</td>
<td>Week 4 neg. (12 weeks)</td>
</tr>
<tr>
<td>Group A</td>
<td>87%</td>
<td>Week 4 pos. (24 weeks)</td>
</tr>
<tr>
<td>Group B</td>
<td>72%</td>
<td>Standard (24 weeks)</td>
</tr>
<tr>
<td>Group B</td>
<td>24/31</td>
<td>Week 4 neg. (12 weeks)</td>
</tr>
<tr>
<td>Group B</td>
<td>9/22</td>
<td>Week 4 pos. (24 weeks)</td>
</tr>
</tbody>
</table>

Summary

Interferon based treatment

Genotype 2, 3

response at week 4

12-16 weeks of antiviral treatment without compromising SVR

non-response at week 4

response at week 24

Extended treatment duration of more than 24 weeks?
New Interferons

• Albinterferon
  – Genetic fusion of Interferon $\alpha$-2b to Albumin
  – longer half-life than pegylated interferon $\alpha$
  – administration every 2 or 4 weeks

• Omega Interferon
  – Naturally occurring Type 1 interferon with 60% homology to interferon $\alpha$
    and 40% homology to interferon $\beta$

• R7025/RO5014583
  – Enhanced interferon molecule generated by gene shuffling technology
  – Optimal pegylation-technology; same pegylation as PEGASYS®

• Lacteron
  – Alpha Interferon (BLX883) released by microspheres
New Antivirals

STAT-C

Specific Targeted Antiviral Therapies for HCV
Replication cycle of HCV

1. binding and internalisation
2. release and uncoating
3. IRES mediated translation
4. polyprotein processing
5. Replication
6. assembly and release

Telaprevir (VX-950)

Telaprevir (VX-950) is an NS3/4A Protease Inhibitor.

HCV-RNA negative (<10 IU/ml) over time:

- **Week 4**
  - Telaprevir plus Peg-IFN α-2a plus Ribavirin: 79%
  - Placebo plus Peg-IFN α-2a plus Ribavirin: 11%

- **Week 12**
  - Telaprevir plus Peg-IFN α-2a plus Ribavirin: 88%
  - Placebo plus Peg-IFN α-2a plus Ribavirin: 52%

- **SVR20**
  - Telaprevir plus Peg-IFN α-2a plus Ribavirin: 67%

*6/9 Pts. with virologic response at wk 4 and stopp treatment at wk 12.*

McHutchison et al. J Hepatol 2007;46:296A
Telaprevir (VX-950) for 14 days

Log$_{10}$ decline of HCV-RNA from baseline

Days of treatment

- Placebo (n=6)
- Breakthrough (n=13)
- Plateau (n=8)
- Cont. Decline (n=7)

Sarrazin et al. 2007;132:1767-77.
Boceprevir (SCH 503034)

**Boceprevir (SCH 503034) 200 mg (n=14)**

-2.45

**Boceprevir (SCH 503034) 400 mg (n=12)**

-1.08

-1.08

-2.88

-1.61

-1.26

-2.5

-2.0

-1.5

-1.0

-0.5

0

log\(_{10}\) decline of HCV-RNA at the end of treatment

Boceprevir plus Peg IFN alfa-2b*

Boceprevir** Peg IFN alfa-2b*

* 2 weeks of treatment,

** 1 week of treatment


NS3/4A Protease Inhibitor
Valopicitabine (NM283)  Nucleoside Type: NS5B  Polymerase Inhibitor

Virologic responders HCV RNA <20 IU/ml [%]

Week 12  Week 24  Week 48

Valopicitabine 200 mg plus Peg IFN alfa-2a (n=34)
Valopicitabine 800 mg plus Peg IFN alfa-2a (n=139)

Lawitz E. et al. J Hepatol 2007;49:9A
Prodrug of nucleoside type polymerase inhibitor R1479

14 days of treatment with R1626 Monotherapy bid

Roberts S et al. Hepatology 2006;44;692A
**Mean log_{10} decline of HCV-RNA**

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype Non-1</th>
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<tbody>
<tr>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>250 mg</td>
<td>250 mg</td>
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<tr>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

**Peg-IFN α-2b plus HCV-796 bid vs. Peg-IFN α-2a for 14 days**

Villano SA et al. J Hepatol 2007;46;24A.
New Antiviral Drugs

- New Interferons (Albinterferon)
- NS3/4A Protease Inhibitors (Telaprevir, Boceprevir)
- NS5B Polymerase Inhibitors
  - Nucleoside Type (Valopicitabine, R1626)
  - Non-Nucleoside Type (HCV-796)
- Other targets: Cyclophilin Inhibitors, alpha glucosidase inhibitor, NS5A Inh.
New Antiviral Drugs - Perspective

• potent antiviral activity

• synergistic antiviral activity with interferon α (and ribavirin?)

• development and selection of resistant variants

• improvement of sustained virologic response rate?

• optimal treatment duration?

• optimal drug combinations?