Clinical management of Hepatitis C infection

1st Asian Conference on Hepatitis B and C, HIV and Influenza, 18-19 May 2012, Beijing, China

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Natural History of HCV Liver Disease

~55-85%

25-30 yrs

2 - 4% / yr

Liver failure (2 – 5% / yr)
Chronic Hepatitis C: Therapy

*HCV therapy is worthwhile*.....
Effective HCV therapy prolongs survival

Cumulative Mortality

Mortality by HCV genotype and response to treatment

At risk:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No SVR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1</td>
<td>7918</td>
<td>4248</td>
</tr>
<tr>
<td></td>
<td>7691</td>
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<td></td>
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<td></td>
<td>344</td>
<td>295</td>
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<tr>
<td>GT2</td>
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<td>2089</td>
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<td>657</td>
<td>1800</td>
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<td>494</td>
<td>1383</td>
</tr>
<tr>
<td></td>
<td>323</td>
<td>951</td>
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<td></td>
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<td>563</td>
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<td>73</td>
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</tr>
<tr>
<td>GT3</td>
<td>697</td>
<td>1097</td>
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<tr>
<td></td>
<td>664</td>
<td>1089</td>
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<tr>
<td></td>
<td>559</td>
<td>931</td>
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<td>293</td>
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<tr>
<td></td>
<td>82</td>
<td>87</td>
</tr>
</tbody>
</table>

Backus et al., Clin Gastroenterol Hepatol 2011
Sustained virological response improves overall survival in chronic hepatitis C patients with advanced fibrosis

529 patients followed for up to 20.2 years (median 7.7 years)

Hazard Ratio of NR vs. SVR

Hazard Ratio’s are adjusted for age, gender, center, fibrosis score, diabetes mellitus, heavy alcohol use and treatment period.
Recommendations

(1) The goal of therapy is to eradicate HCV infection (A1).
(2) The endpoint of therapy is sustained virological response (A1). Once obtained, SVR usually equates to cure of infection in more than 99% of patients (A1).
(3) Intermediate endpoints to assess the likelihood of an SVR are HCV RNA levels at 4, 12, and 24 weeks of therapy (B2).
Definitions of virological response at week 4 and week 12

- **RVR**: undetectable HCV RNA at week 4
- **cEVR**: no RVR but undetectable HCV RNA at week 12
- **pEVR**: no RVR and detectable HCV RNA, but >2 log\(_{10}\) drop at week 12

RVR - Rapid virological response; cEVR – complete Early virological response; pEVR - partial Early virological response; SVR – Sustained virologic response
Recommendations

(1) Liver disease severity should be assessed prior to therapy (B1).
(2) Identifying patients with cirrhosis is of particular importance, as their prognosis and likelihood to respond to therapy are altered, and they require surveillance for HCC (A1).
(3) As liver disease can progress in patients with repeatedly normal ALT levels, disease severity evaluation should be performed regardless of ALT levels (B2).
(4) Assessment of the severity of liver fibrosis is important in decision making in patients with chronic hepatitis C (A1).
(5) Liver biopsy is still regarded as the reference method to assess the grade of inflammation and the stage of fibrosis (A2).
(6) Transient elastography (TE) can be used to assess liver fibrosis in patients with chronic hepatitis C (A2).
(7) Non-invasive serum makers can be recommended for the detection of significant fibrosis (METAVIR score F2–F4) (A2).
Chronic Hepatitis C: Improvement by trial and error

Optimization of dose and duration

- IFN 24 weeks
- IFN 48 weeks
Chronic Hepatitis C: Improvement by trial and error

One unspecific drug plus another unspecific drug = highly effective therapy

Sustained virological response

IFN & Ribavirin 48 weeks
IFN 48 weeks
IFN 24 weeks

>50% cure of chronic Hepatitis C

Sustained virological response

- IFN & Ribavirin 48 weeks
- IFN 48 weeks
- IFN 24 weeks
- PEG IFN & Ribavirin
- PEG-IFN 48 weeks
  - 12 kDa PEG-IFN alfa-2b
  - 40 kDa PEG-IFN alfa-2a
Not all patients have the same likelihood of achieving an SVR.

Negative Prognostic Factors

- Age
- HIV Co-infection
- High Viral load
- IL28B T allele
- ESRD
- Gender
- Alcohol
- Obesity
- Diabetes
- Race
- Cirrhosis
- HCV genotype 1 and 4

SVR – Sustained virologic response, ESRD – End-stage renal disease, IL28B – Interleukin 28B.
PROPHESYS Study:
Virological Response Varied by Genotype: G1 and G4

The error bars correspond to the 95% confidence intervals
Virological response defined as: HCV RNA <50 IU/mL

Marcellin P et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 73
PROPHESYS Study: Virological Response Varied by Genotype: G2 and G3

Virological response defined as: HCV RNA <50 IU/mL

Marcellin P et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 73

The error bars correspond to the 95% confidence intervals.
Impact of fibrosis on treatment outcome (PROPHESYS study)

A

<table>
<thead>
<tr>
<th>METAVIR Score</th>
<th>Patients with an RVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0 (n=63)</td>
<td>31.7</td>
</tr>
<tr>
<td>F1/2 (n=892)</td>
<td>28.1</td>
</tr>
<tr>
<td>F3 (n=495)</td>
<td>23.2</td>
</tr>
<tr>
<td>F4 (n=142)</td>
<td>15.5</td>
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<tr>
<td>≤0.5 (n=154)</td>
<td>39.0</td>
</tr>
<tr>
<td>&gt;0.5–1.5 (n=870)</td>
<td>27.2</td>
</tr>
<tr>
<td>&gt;1.5–3.0 (n=402)</td>
<td>19.9</td>
</tr>
<tr>
<td>&gt;3.0 (n=166)</td>
<td>18.7</td>
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B

<table>
<thead>
<tr>
<th>METAVIR Score</th>
<th>Patients with an SVR (%)</th>
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<tbody>
<tr>
<td>F0 (n=63)</td>
<td>58.7</td>
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<tr>
<td>F1/2 (n=892)</td>
<td>44.8</td>
</tr>
<tr>
<td>F3 (n=495)</td>
<td>38.0</td>
</tr>
<tr>
<td>F4 (n=142)</td>
<td>18.3</td>
</tr>
<tr>
<td>≤0.5 (n=154)</td>
<td>63.6</td>
</tr>
<tr>
<td>&gt;0.5–1.5 (n=870)</td>
<td>43.6</td>
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<tr>
<td>&gt;1.5–3.0 (n=402)</td>
<td>33.3</td>
</tr>
<tr>
<td>&gt;3.0 (n=166)</td>
<td>24.1</td>
</tr>
</tbody>
</table>

Ferenci P, et al. AASLD.2011
IL28B polymorphism and treatment outcome

Percentage of SVR by genotypes of rs12979860.

Sampling locations, allele frequencies and degree of regional differentiation of the rs12979860 C allele.


SVR – Sustained virologic response
SVR in relation to IL28B (rs12979860), fibrosis grade and baseline viral load (GT1)

RVR - Rapid virological response; cEVR – complete Early virological response; SVR – Sustained virologic response

Standard therapy in HCV genotyp 2/3

- Treatment start HCV-RNA-level
  - Week 4 HCV-RNA-determination
  - HCV-RNA < 12-15 IU/ml
    - Initial HCV-RNA < 8x 10^5 IU/ml
      - 16 weeks of therapy
    - HCV-RNA < 12-15 IU/ml
      - 24 weeks of therapy
  - HCV-RNA < 12-15 IU/ml
    - Week 12 HCV-RNA-determination
      - Δ HCV-RNA > 12-15 IU/ml
        - 48 weeks of therapy
      - Δ HCV RNA* < 2 log
    - Consensus: 100%

- Treatment discontinuation
- No shortened duration for F3/F4 Metabolic Syndrom
- No data for normal transaminases
- *extended therapy in case of slow response is currently studied

Z Gastroenterol 2010; 48:289–351
Standard therapy in HCV genotyp 1/4

- Treatment start
  - HCV-RNA-level

- Week 4
  - HCV-RNA-determination
  - HCV-RNA < 12-15 IU/ml + Initial HCV-RNA * < 6-8x 10^5 IU/ml

- Week 12
  - HCV-RNA-determination
  - HCV-RNA < 12-15 IU/ml

- Week 24
  - HCV-RNA-determination
  - HCV-RNA < 12-15 IU/ml

- HCV RNA > 2 log or > 3x10^4 IU/ml
- HCV RNA pos

- Consensus: 98%
- Treatment discontinuation

* 6x10^5 IU/ml pegIFN α2b
  8x10^5 IU/ml pegIFN α2a
  No shortened duration for F3/F4
  Metabolic Syndrom
  No data for normal transaminases

Z Gastroenterol 2010; 48:289–351
The new DAAs

Entry-Inhibitors

Ribavirin

Protease-Inhibitors

Cyclophilin Inhibitors

NS5A-Inhibitors

Polymerase inhibitors

NI

NNI

TLR-Agonists
Therapeutic Vaccine
Other IFNs
PEG-IFN lambda

**Boceprevir (Victrelis)**
FDA approval 13.5.2011
Europe: 18.7.2011

4x200 mg every 7-9h
*With a meal*
(3X4 tablets)

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**Telaprevir (Incivek)**
FDA approval 23.5.2011
Europe: 20.9.2011

2x325 mg alle 7-9h
*With a fatty meal*
(3X2 tablets)
Improved SVR rates for GT1 patients with Triple Therapy

Poordad et al., NEJM 2011;364:1195-1206
Tolerability

- Discontinuation rates higher in PI arms
- Telaprevir
  - Pruritus, nausea, rash, anemia, and diarrhea
  - Severe rash in 3-6% (1% PEG/RBV)
    - 5-7% stop TVR; 1% stop treatment
  - Hgb <10g/dl: 35-45% vs. 14% [ESA use not allowed]
- Boceprevir
  - Anemia, dysgeusia
  - Hgb <10g/dl: 50% vs. 18%
    - Erythropoietin use: 43% vs. 24%
<table>
<thead>
<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Telaprevir n=296</th>
<th>Boceprevir n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (%)</td>
<td>48.6</td>
<td>38.4</td>
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<tr>
<td>Premature discontinuation</td>
<td>26.0</td>
<td>23.9</td>
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<tr>
<td>Due to SAEs (%)</td>
<td>14.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Death (%)</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Infection (Grade 3/4) (%)</td>
<td>8.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Asthenia (Grade 3/4) (%)</td>
<td>4.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4 (SCAR) (%)</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus (Grade 3/4) (%)</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Hepatic decompensation (%)</td>
<td>4.4</td>
<td>4.4</td>
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# CUPIC: Preliminary Safety Findings

<table>
<thead>
<tr>
<th>Patients, n (% patients with at least one event)</th>
<th>Telaprevir (n=296)</th>
<th>Boceprevir (n=159)</th>
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</thead>
<tbody>
<tr>
<td><strong>Anemia (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Grade 2 (8.0 – &lt;10.0 g/dL)</td>
<td>19.6</td>
<td>22.6</td>
</tr>
<tr>
<td>Grade 3/4 (&lt;8.0 g/dL)</td>
<td>10.1</td>
<td>10.1</td>
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<tr>
<td>EPO use</td>
<td>56.8</td>
<td>66.0</td>
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<tr>
<td>Blood transfusion</td>
<td>15.2</td>
<td>10.7</td>
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<tr>
<td><strong>Neutropenia (%)</strong></td>
<td></td>
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<tr>
<td>Grade 3 (500 – &lt;1000/mm³)</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Grade 4 (&lt;500/mm³)</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>G-CSF use</td>
<td>2.4</td>
<td>3.8</td>
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<tr>
<td><strong>Thrombopenia (%)</strong></td>
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<tr>
<td>Grade 3 (25 000 – &lt;50 000)</td>
<td>11.8</td>
<td>6.3</td>
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<tr>
<td>Grade 4 (&lt;25 000)</td>
<td>1.3</td>
<td>0.6</td>
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<tr>
<td>Thrombopoïetin Use</td>
<td>1.7</td>
<td>1.9</td>
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CUPIC: Telaprevir Preliminary Efficacy Data

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<tr>
<th>Week</th>
<th>% of Patients with Undetectable HCV RNA</th>
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<tbody>
<tr>
<td>Week 4</td>
<td>53/276, 51/285</td>
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<tr>
<td>Week 8</td>
<td>85/265, 79/282</td>
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<tr>
<td>Week 12</td>
<td>86/254, 78/281</td>
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<tr>
<td>Week 16</td>
<td>86/205, 71/251</td>
</tr>
</tbody>
</table>

Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.
CUPIC: Boceprevir Preliminary Efficacy Data

% of Patients with Undetectable HCV RNA

<table>
<thead>
<tr>
<th>Week</th>
<th>% Patients</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>1/155</td>
</tr>
<tr>
<td>8</td>
<td>55/149</td>
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<tr>
<td>12</td>
<td>88/144</td>
</tr>
<tr>
<td>16</td>
<td>89/126</td>
</tr>
</tbody>
</table>

Hezode C et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 8.
Treatment algorithm for triple HCV therapy with boceprevir (BOC)

- **Naive Pat. with RVR**
  - 24 weeks BOC + PegIFN/RBV

- **Naive Pat. Without RVR**
  - 32 weeks BOC + PegIFN/RBV

- **Previous relapsers**
  - 32 weeks BOC + PegIFN/RBV

- **Non-responders + All cirrhosis**
  - 48 weeks BOC + PegIFN/RBV
Treatment algorithm for triple HCV therapy with telaprevir (TVR)
Futility rules

Initial HCV RNA decline provides information on treatment prediction outcome

PEG-IFN+RBV

Telaprevir

- HCV-RNA >1000 IU/ml → Stop
- HCV-RNA >1000 IU/ml → Stop
- HCV-RNA >20 IU/ml → Stop

PEG-IFN+RBV

Boceprevir

- Initial HCV RNA >100 IU/ml → Stop
- HCV-RNA >20 IU/ml → Stop

Hivbook 2012 in press; Hivbook.com
Electron Study: Treatment with GS-7977

- **GT 2/3 Treatment-Naïve**: 
  - Week 0: GS-7977 + RBV
  - Week 4: GS-7977 + RBV
  - Week 8: GS-7977 + RBV
  - Week 12: GS-7977 + RBV
  - n=10

- **GT 2/3 Tx-naive**
  - Week 0: GS-7977 + PEG + RBV
  - Week 4: GS-7977 + PEG + RBV
  - Week 8: GS-7977 + PEG + RBV
  - Week 12: GS-7977 + PEG + RBV
  - n=9

- **GT 2/3 Treatment-Naïve (GS-7977 + RBV + PEG)**
  - Week 0: GS-7977 + PEG + RBV
  - Week 4: GS-7977 + PEG + RBV
  - Week 8: GS-7977 + PEG + RBV
  - Week 12: GS-7977 + PEG + RBV
  - n=11

- **GS-7977**
  - Week 0: GS-7977
  - Week 4: GS-7977
  - Week 8: GS-7977
  - Week 12: GS-7977
  - n=10

- **GT 2/3 Treatment-Null Responders (GT 1 Null Responders)**
  - Week 0: GS-7977 + RBV
  - Week 4: GS-7977 + RBV
  - Week 8: GS-7977 + RBV
  - Week 12: GS-7977 + RBV
  - n=10

- **GT 2/3 Treatment-Naïve (GT 1 Treatment-Naïve)**
  - Week 0: GS-7977 + RBV
  - Week 4: GS-7977 + RBV
  - Week 8: GS-7977 + RBV
  - Week 12: GS-7977 + RBV
  - n=25

- **GT 2/3 Treatment-Experienced (GT 2/3 Treatment-Experienced)**
  - Week 0: GS-7977 + RBV
  - Week 4: GS-7977 + RBV
  - Week 8: GS-7977 + RBV
  - Week 12: GS-7977 + RBV
  - n=25

Gane E, et al. 47th EASL; Barcelona, Spain; April 18-22, 2012. Abst. 1113.
Electron Study: Virologic Response

<table>
<thead>
<tr>
<th></th>
<th>GT 2/3 Treatment-naïve 8 wks (N=10)</th>
<th>GT 1 Null Responders 12 wks (N=10)</th>
<th>GT 1 Treatment-naïve 12 wks (N=25)</th>
<th>GT 2/3 Treatment-experienced 12 wks (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 1</strong></td>
<td>6/10 (60)</td>
<td>1/10 (10)</td>
<td>7/25 (29)</td>
<td>8/25 (32)</td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td>10/10 (100)</td>
<td>7/10 (70)</td>
<td>17/24 (71)</td>
<td>21/25 (84)</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>10/10 (100)</td>
<td>10/10 (100)</td>
<td>25/25 (100)</td>
<td>25/25 (100)</td>
</tr>
<tr>
<td><strong>EOT</strong></td>
<td>10/10 (100)</td>
<td>9/9 (100)</td>
<td>25/25 (100)</td>
<td>21/21 (100)</td>
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<tr>
<td><strong>SVR 4</strong></td>
<td>10/10 (100)</td>
<td>1/9 (11)</td>
<td>22/25 (88)</td>
<td>12/15 (80)</td>
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<tr>
<td><strong>SVR 8</strong></td>
<td>10/10 (100)</td>
<td>1/9 (11)</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>SVR 12</strong></td>
<td>10/10 (100)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Patients with HCV RNA <LOD Over Time, n/N (%)
“Individualized” Therapy of Hepatitis C in 2012

F0/F1, CI for IFNa
Other reasons against therapy

Therapy-indication
Therapy wish

Neg. Factors
SVR-Chance <10%

PEG_IFNa/RBV
Lead-in

continue
PEG-IFN/RBV

RG-Triple-Therapy

Therapy-discontinuation

For now no therapy

IFN-free Therapy in 2014/5

Futility rules

No SVR

SVR

Wedemeyer et al., DMW 2012