Hepatitis C: Management of Treatment Naïve Patients with First Line Protease Inhibitors

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To Treat or Not to Treat

- 35-year-old mother of 3 young children
- Transmission date and mechanism unknown
- No previous treatment
- Transaminases normal for 3 years
- No extrahepatic symptoms, no other relevant diseases
The Patient with Mild Disease

- No alcohol, no psychiatric history
- Physical examination normal
- Body mass index 31.5 kg/m²
- *IL-28b* genotype CC
- HCV genotype 1b
- Viral load 210,00 IU/L
- Liver biopsy stage F1
- Hemoglobin 13.5 g/dL
- Motivated to be treated
The Patient with Mild Disease

• Questions patient asks:
  
  – “Can I take any currently approved PI twice per day instead of 3 times per day?”
  
  – “Should I evaluate my interferon responsiveness with 4 weeks of PEG/RBV before starting a PI?”
  
  – “What is my optimal duration of therapy?”
  
  – “How early can nonresponse be predicted?”
Phase III, randomized, open-label, international, non-inferiority study examining telaprevir bid vs q8h, when administered with PR (N=740)

- Treatment-naïve patients with genotype 1 HCV
- Stratified by fibrosis stage and \( IL-28B \) genotype
- RGT based on response at Week 4 (RVR)

**OPTIMIZE: Study Design**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12(bid)/PR n=369</td>
<td>TVR + PR</td>
</tr>
<tr>
<td>T12(q8h)/PR n=371</td>
<td>TVR + PR</td>
</tr>
</tbody>
</table>

OPTIMIZE: Telaprevir BID was Non-Inferior to Q8H in Terms of SVR

All patients received TVR/PEG/RBV

Difference 1.5% (95% CI: –4.9%, 12.0%)

274/369

74

T12(BID)/PR

270/371

73

T12(Q8H)/PR

All patients received TVR/PEG/RBV

OPTIMIZE: SVR12 by Cirrhosis Status

Horsmans Y, et al. EASL 2013; Abstract 826
12 WEEK RESULTS:
A PEEK INTO THE NEAR FUTURE
NEUTRINO: Sofosbuvir/IFN/RBV x 12 Weeks: SVR Independent of Baseline Factors

Lawitz E, et al. EASL 2013, Amsterdam, #1411; Lawitz E et al NEJM April 2013
## OPTIMIZE: Adverse Events

### Preferred term, n (%)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>T12(BID)/PR N=369</th>
<th>T12(Q8H)/PR N=371</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>360 (98)</td>
<td>367 (99)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>28 (8)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Death*</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Any Grade ≥3 adverse event</td>
<td>156 (42)</td>
<td>139 (38)</td>
</tr>
<tr>
<td>Grade ≥3 anemia SSC</td>
<td>95 (26)</td>
<td>70 (19)</td>
</tr>
<tr>
<td>Grade ≥3 rash SSC</td>
<td>18 (5)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Any Grade 4 adverse event</td>
<td>23 (6)</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Any adverse event leading to permanent discontinuation of telaprevir</td>
<td>57 (15)</td>
<td>69 (19)</td>
</tr>
</tbody>
</table>

### Response by Metavir fibrosis stage/cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>TVR Q8H n=371</th>
<th>TVR BID n=369</th>
<th>All patients N=740</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB &lt;8.5 g/dL, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0–2</td>
<td>26/250 (10)</td>
<td>35/256 (14)</td>
<td>61/506 (12)</td>
</tr>
<tr>
<td>F3/4</td>
<td>16/108 (15)</td>
<td>30/100 (30)</td>
<td>47/208 (22)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4/49 (8)</td>
<td>15/54 (28)</td>
<td>19/103 (18)</td>
</tr>
<tr>
<td>Without cirrhosis</td>
<td>38/309 (12)</td>
<td>50/302 (17)</td>
<td>88/611 (14)</td>
</tr>
</tbody>
</table>

The Patient with Mild Disease

- Sophisticated patient wants to know
  - “Can I take any currently approved PI twice per day instead of 3 times per day?”
  - “Should I evaluate my interferon responsiveness with 4 weeks of PEG/RBV before starting a PI?”
  - “What is my optimal duration of therapy?”
  - “How early can nonresponse be predicted?”
Boceprevir: SVR and Lead-In Response

The Patient with Mild Disease

• Sophisticated patient wants to know
  – “Can I take any currently approved PI twice per day instead of 3 times per day?”
  – “Should I lead in with PEG/RBV before starting a PI?”
  – “What is my optimal duration of therapy?”
  – “How early can nonresponse be predicted?”
CONCISE Interim Analysis: High SVR rates for 12-week Total TVR Combination Therapy in IL28B CC Treatment-Naives and Prior Relapsers With G1 Chronic Hepatitis C

Summary of hemoglobin levels during the 12-week TVR treatment phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Randomized</th>
<th>Safety population N=239</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T12/PR12</td>
<td>T12/PR24</td>
</tr>
<tr>
<td>Hemoglobin, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 g/dL</td>
<td>54 (51)</td>
<td>23 (44)</td>
</tr>
<tr>
<td>&lt;8.5 g/dL</td>
<td>14 (13)</td>
<td>8 (15)</td>
</tr>
</tbody>
</table>

Sustained virologic response at Weeks 4 and 12 for randomized patients treated with T12/PR12 and T12/PR24

<table>
<thead>
<tr>
<th></th>
<th>Patients with SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR4</td>
</tr>
<tr>
<td>T12/PR12</td>
<td>89% (93/104)</td>
</tr>
<tr>
<td>T12/PR24</td>
<td>100% (38/38)</td>
</tr>
</tbody>
</table>

Nelson DR, et al. EASL 2013, Amsterdam, #881
The Patient with Mild Disease

Questions patient asks:

- “Can I take any currently approved PI twice per day instead of 3 times per day?”
- “Should I evaluate my interferon responsiveness with 4 weeks of PEG/RBV before starting PI?”
- “What is my optimal duration of therapy?”
- “How early can nonresponse be predicted?”
Aim: To investigate the clinical relevance of early genotypic resistance test in G1 patients with advanced disease treated with triple therapy by population and ultra-deep sequencing. 2 weeks HCV RNA values >100 IU/mL are associated with virologic breakthrough.

10 patients with TND
HCV RNA values at Week 2: 0 failures

18 patients with <100 IU/mL
HCV RNA at Week 2: 1 failure

15 patients with >100 IU/mL
HCV RNA at Week 2: 8 failures

p=0.001
TND, target not detected

Cento V, et al. EASL 2013, Amsterdam, #63
Virologic failure to TVR with the appearance of V36M + R155K in a patient infected with G1a showing at 48h minor resistance variants

<table>
<thead>
<tr>
<th>ID_13</th>
<th>HCV G1a</th>
<th>Age: 43</th>
<th>Sex: M</th>
<th>Null responder to SOC</th>
<th>IL28: CT</th>
</tr>
</thead>
</table>

Log HCV RNA (IU/mL)

- TVR + PegIFN-2α + RBV
- PegIFN-2α + RBV
- No treatment

GRT Day 0
NS3=protease: None

GRT 48h
NS3=protease: None
By UDPs: V36A 2.3%, R155K 4.3%
Mutational load: V36A=182 IU/mL R155K=301 IU/mL

GRT 18 weeks
NS3=protease: V36M, R155K

GRT 30 weeks
NS3=protease: V36M, R155K

PI interruption

LLOQ (15 IU/mL)
LLOD (10 IU/mL)

Cento V, et al. EASL 2013, Amsterdam, #63
Summary

• First generation protease inhibitors are a significant advance in hepatitis C therapy
• Evaluate baseline predictors of IFN-responsiveness
• Although newer therapies are on the horizon, IFN-responsive patients can achieve high rates of SVR today
• The longer a patient remains viremic while on therapy, the more likely virologic failure will occur
• New therapies are on the horizon thus discussions with patients about risks, benefits and alternatives are important