HEPATITIS-C WORKSHOP
HOW TO USE TRIPLE THERAPY FOR GENOTYPE1 HCV INFECTION
(4) 16:00-17:30  Hall 5

16:00  HCW4-01
PI-Triple Therapy in Liver Transplant Recipients
N. Terrault, San Francisco, CA, USA
PI Triple Therapy
Treatment of Post Liver Transplant Recipients

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Post-Transplant Survival Reduced in HCV Transplant Recipients

Recipients with HCV have 30% higher mortality at 5 years

ELTR- 01/1988 - 12/2001
Natural History of HCV Disease in Liver Transplant Recipients

- Up to 10% develop severe, early recurrence including fibrosing cholestatic hepatitis → graft loss within first few years
- On average, 20-30% develop recurrent cirrhosis within 5 years
  - High risk: older donors, HIV+, African-Americans
- Median time to cirrhosis = 8-10 years
  - Time to reach cirrhosis decreasing over time

Limited time to intervene to prevent graft loss

Aytaman A, Curr Opin Organ Transplant 2010;16:301-9
Clinical Benefits of Antiviral Therapy

- Treated patients have superior survival to untreated matched controls
- Differences in survival even greater if SVR achieved

Berenguer M, Am J Transplant 2008
Picciotto FP. J Hepatol 2007
PI-Triple Therapy for Management of HCV in LT Recipients

- Prevent graft infection
- Prevent HCV disease
- Prevent cirrhosis and graft failure
- Antiviral therapy for recurrent disease

Listed

Option for select patients
- LDLT
- HCC

Transplant

Preemptive Antiviral Therapy (started at LT or shortly thereafter)

Chronic hepatitis

Primary treatment strategy

Graft loss

Prevent HCV disease

Prevent HCV disease

Prevent HCV disease
Indications for Treatment Based by Histologic Disease Severity

- Fibrosing cholestatic hepatitis
- Fibrosis ≥F2 (scale of 4)
- Grade ≥ A3 (scale of 4)

# Efficacy of Post-Transplantation Peg-IFN and RBV

## Results of Systematic Reviews

<table>
<thead>
<tr>
<th>Author</th>
<th>Years included</th>
<th>N (# per study)</th>
<th>SVR Overall</th>
<th>SVR G1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>1980-2005</td>
<td>587 (11-86)</td>
<td>27%</td>
<td>--</td>
</tr>
<tr>
<td>Berenguer</td>
<td>2002-2006</td>
<td>611 (12-61)</td>
<td>30%</td>
<td>29%</td>
</tr>
<tr>
<td>Xirouchakis</td>
<td>1999-2008</td>
<td>264* (13-54)</td>
<td>44% (ARR 31%)</td>
<td>32%</td>
</tr>
</tbody>
</table>

*Controlled trials, peginterferon and ribavirin vs low dose or no treatment

*Wang, Am J Transpl 2006; Berenguer, J Hepatol 2008; Xirouchakis, J Viral Hep 2008*
Adverse Events associated with PegIFN-Ribavirin

- Dose reductions very frequent ~70-80%
  - Mainly due to hematologic toxicity
  - Growth factor use common
  - Transfusion: 7%

- Premature treatment discontinuation
  - 43-52%, mainly due to anemia
  - Other reasons (psych issues, infections, asthenia)

- Rejection
  - Acute = 4-11%; Severe = 5%
  - Chronic rejection = 2%

- De novo “autoimmune hepatitis” 6%
PI-Triple Therapy in Liver Transplant Recipients

- PI-triple therapy expected to increase the proportion of patients achieving viral clearance
  - Limited data on SVR rates in LT recipients

- Considerations with use of PI-triple therapy
  - Genotype 1 only
  - Less effective in prior partial and null-responders to peg-IFN and RBV
  - More drugs = more side effects → especially anemia
  - Drug interactions (PIs and CNIs/sirolimus)
Drug-Drug Interactions

- TPV and BOC block CYP 3A4 and P-glycoprotein → CSA, TAC, Sirolimus levels increase

<table>
<thead>
<tr>
<th>Healthy Volunteer Study</th>
<th>Effect on CsA levels</th>
<th>Effect on Tac levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>4.6-fold increase</td>
<td>70-fold increase</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>2.7-fold increase</td>
<td>17-fold increase</td>
</tr>
</tbody>
</table>

- DDI studies not done with sirolimus

- Neither cyclosporine nor tacrolimus affected telaprevir or boceprevir levels

*Hulskotte, Hepatology 2012; Garg, Hepatology 2011*
Strategies for Management of CNI – PI Interactions

- Convert from tacrolimus to cyclosporine prior to start of treatment
  - Most applicable if telaprevir used
  - Stable trough levels for 4 weeks
- Intensive monitoring when starting and stopping the PI
  - Must use lab that have rapid turnaround for CNI levels
  - Twice weekly minimum; most use daily for first 5 days
- CNI trough levels may decline during treatment (in context of HCV response) and dose upward adjustments needed to minimize rejection risk
# Strategies for Management of CNI – PI Interaction

<table>
<thead>
<tr>
<th>Week</th>
<th>Cyclosporine conversion</th>
<th>Peginterferon-alfa 2a</th>
<th>Ribavirin</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0</td>
<td>Dose: reduced to 75% Interval: decreased to daily (q24hr)</td>
<td>starting dose: 135 mcg weekly</td>
<td>starting dose: 800 mg/d (GFR ≥60), 400-600 mg/d (GFR 30-59), 200 mg TIW - 200mg/d (GFR &lt;30)</td>
<td>750 mg every 7-9 hours Taken with food and no dose reduction</td>
</tr>
<tr>
<td>Wk 4</td>
<td>Dose: resumed pre-TVIR dose Interval: increased to q12hr</td>
<td>target dose: 180 mcg weekly</td>
<td>target dose: 1,000 mg/d (weight &lt;75kg), 1,200 mg/d (weight ≥75kg)</td>
<td></td>
</tr>
<tr>
<td>Wk 12</td>
<td></td>
<td></td>
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<tr>
<td>Wk 16</td>
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<tr>
<td>Wk 20</td>
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<tr>
<td>Wk 24</td>
<td></td>
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<tr>
<td>Wk 48</td>
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Pangapong, Liver Transplant 2013
Calcineurin Inhibitor Dosing With Tacrolimus

- 75% reduction
- 88% reduction

Verna E, EASL 2013
# Early Experience with PI-Triple Therapy in LT Recipients*

- First published report by Werner et al: N=9 patients treated with TVR triple therapy
  - RVR = 4/9 (44%) and EVR 8/9 (89%)

<table>
<thead>
<tr>
<th>Country, Author</th>
<th>N</th>
<th>PI used</th>
<th>RVR</th>
<th>EVR</th>
<th>SVR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>France Coilly</td>
<td>25</td>
<td>BOC 54% TVR 46%</td>
<td>BOC 43% TVR 45%</td>
<td>BOC 79% TVR 73%</td>
<td>--</td>
</tr>
<tr>
<td>USA Pungapong</td>
<td>26</td>
<td>TVR</td>
<td>15%</td>
<td>68%</td>
<td>--</td>
</tr>
<tr>
<td>USA CRUSH-C</td>
<td>112</td>
<td>BOC 10% TVR 90%</td>
<td>66%</td>
<td>84%</td>
<td>68% (N=43)</td>
</tr>
</tbody>
</table>

*Limited to studies of ≥25 patients and reported VR to week 12 of PI therapy

CRUSH-C: Early Viral Dynamics

- Multicenter study, 101 HCV-infected G1 LT recipients
- PI used: 90% telaprevir and 10% boceprevir
- P+R lead-in (LI) used in 96%

Median HCV RNA (log units) IU/mL

- Median 1.5 log decline
- 61% had ≥1 log decline

- Median 3.8 log decline

Verna E, EASL 2013
HCV PI Therapy for HCV Recurrence Following LT: French Experience

56-70% of patients achieved HCV RNA undetectability by week 8 of treatment

Mean duration therapy 20.3 mos

CRUSH-C Study
Sustained Virologic Response

- 43 patients with opportunity for SVR4

Verna E, EASL 2013
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Patients (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE requiring Rx discontinuations</td>
<td>11%</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>21%</td>
</tr>
<tr>
<td>Transfusion (%)</td>
<td>46</td>
</tr>
<tr>
<td>Number of units**</td>
<td>2 (1-15)</td>
</tr>
<tr>
<td>Rash (%)*</td>
<td>7%</td>
</tr>
<tr>
<td>Cr increase &gt;0.5 mg/dl (%)</td>
<td>34%</td>
</tr>
<tr>
<td>Rejection**</td>
<td>4%</td>
</tr>
<tr>
<td>Death</td>
<td>6%</td>
</tr>
<tr>
<td>Liver-related</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Rash requiring more than topical therapy
**Any treated rejection during or after TT
PI Triple Therapy in Transplant Recipients

- **Positives:**
  - Higher response rates likely

- **Negatives**
  - Side effects greater
  - D/C rates higher → reduced SVR rates
  - Significant DDI (post-LT) → kidney risks, rejection
  - Non-responders have PI resistance – consequences unknown
Glimpse of Future Treatment for Post-LT HCV Disease
Case Report of Sofosbuvir plus Daclatasvir

- G1b severe cholestatic HCV at 6 mos post-LT
  - AST 503 IU/mL, ALKP 298 IU/mL → typical histologic picture
  - Decompensated with development of ascites
  - HCV RNA 12 million IU/mL, LI28B CT
- Sofosbuvir (400 mg/day) + daclatasvir (60 mg/day) co-administered for 24 wks
  - Obtained on emergency basis
  - IRB approved protocol

- Week 4: HCV RNA (-) normal biochemistry and ascites resolved
- During treatment and follow-up: stable tacrolimus dose and levels
  - 1 year F/U: SVR with normal liver tests

PI Triple Therapy in LT Recipients

Summary

- PI–CNI/mTOR drug interactions require close monitoring but are management
- PI-triple therapy achieves:
  - High rates of on-treatment virologic response
  - SVR rates ~60% (~2-fold higher than with Peg-IFN /RBV)

But ..... with a substantially higher rate of side effects

- Other DAA combos needed to increase efficacy and improve tolerability