HCV Management
After the Hype
Addressing the Realities of the DAA Era
Massimo Puoti
AO Ospedale Niguarda Ca’ Granda  Milano, Italy
Disclosures

• Member of advisory boards &/or speaker in own events &/or investigator in RCT &/or research grants &/or teacher during courses for employees for
## Viral Genotypes and Response to PEG-IFN and Ribavirin

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
<th>Genotype 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVR</strong></td>
<td><strong>SVR</strong></td>
<td><strong>SVR</strong></td>
<td><strong>SVR</strong></td>
</tr>
<tr>
<td>45%–55%</td>
<td>75%–80%</td>
<td>60%–75%</td>
<td>40%–60%</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>15%–25%</td>
<td>10%–20%</td>
<td>15%–25%</td>
</tr>
<tr>
<td>20%–30%</td>
<td>&lt; 5%</td>
<td>10%–20%</td>
<td>Discontinue 20%</td>
</tr>
<tr>
<td><strong>Discontinue</strong></td>
<td>5-10%</td>
<td>NR 10-15%</td>
<td>Discontinue 20%</td>
</tr>
<tr>
<td>20%</td>
<td>NR 5%</td>
<td>10%–15%</td>
<td>Relapse 15%–25%</td>
</tr>
<tr>
<td>NR 20%</td>
<td>Discontinue 5-10%</td>
<td>NR 10-15%</td>
<td>Discontinue 20%</td>
</tr>
</tbody>
</table>

**Low viral load /HCV RNA < 400,000 IU affect SVR:** ++ G1, +/- G2, + G3, ? G4
Response-guided therapy in patients with genotypes 2 and 3

*Marginally less effective due to higher relapse rates, especially for G3 with high viral load.

SVR Rates With PI: BOC or TVR in Genotype 1 Treatment-Naive Patients

<table>
<thead>
<tr>
<th>Therapy vs PR 48w</th>
<th>Relative Risk 95% CI</th>
<th>Events Treatment n/N</th>
<th>Events Control n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBOC x 48w</td>
<td>1.81 (1.58-2.06)</td>
<td>319/469</td>
<td>176/467</td>
</tr>
<tr>
<td>PRTVR x 48 w</td>
<td>1.48 (1.26-1.75)</td>
<td>196/286</td>
<td>100/220</td>
</tr>
</tbody>
</table>

Chou R et al. Ann Int Med 2013; 158; 114-123
SVR Rates With BOC or TVR in Genotype 1 Treatment-Experienced Patients

After the Hype
Addressing the Realities of the DAA Era

• New Challenges of anti HCV therapy
  – Complex schedule
  – Drug costs
  – Categorizing previous treatment response
  – Adherence & DDI
  – Resistance
  – Side effects

• The realities of special populations
  – Cirrhosis
  – HIV
  – Liver transplant recipients
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Telaprevir in Genotype 1 Patients

- 750 mg (two 375-mg tablets) q8hr with food (not low fat; standard fat meal is 21 g)

Treatment Naive and Previous Relapsers

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criterion</th>
<th>Stopping Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4 or 12</td>
<td>HCV RNA &gt; 1000 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>Detectable HCV RNA</td>
<td>Discontinue PR</td>
</tr>
<tr>
<td>Any</td>
<td>Discontinuation of PR for any reason</td>
<td>Discontinue TVR</td>
</tr>
</tbody>
</table>

Previous Partial or Null Responders

eRVR: HCV RNA undetectable at 4 & 12 weeks

**Boceprevir in Genotype 1 Patients**

- 800 mg (four 200-mg capsules) q8hr with meal or light snack

**Treatment Naïve w/o cirrhosis**

- **PR**
  - BOC + PR
  - Early response stop at Wk 28: 59%

**Previous Relapsers or Partial Responders w/o cirrhosis**

- **PR**
  - BOC + PR
  - PR

**Pts with cirrhosis or Null Responders**

- **PR**
  - BOC + PR

**Early response: HCVRNA undetectable at 8 & 24 weeks**

- All cirrhotic patients should receive lead-in followed by PR + BOC for 44 wks
- If considered for treatment, null responders should receive lead-in then PR + BOC for 44 wks
- EMA label recommends fixed-duration therapy for all trt-expd patients: LI + 32 wks triple + 12 wks PR

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Criterion</th>
<th>Stopping Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 12</td>
<td>HCV RNA ≥ 100 IU/mL</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Wk 24</td>
<td>Detectable HCV RNA</td>
<td>Discontinue all therapy</td>
</tr>
<tr>
<td>Any</td>
<td>Discontinuation of PR for any reason</td>
<td>Discontinue BOC</td>
</tr>
</tbody>
</table>

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Costs

• Boceprevir & Telaprevir: high cost drugs
• Heterogeneous prevalence of Hepatitis C ranging from 0,5% to 2.5% → country specific impact on health budgets
• Competition with other innovative high cost drugs (i.e. biologic drugs for immune mediated diseases, anticancer drugs) in the scenario of an economic crisis
• Optimization of patients selection for cost/effectiveness
  – Sickest first but lack of data on safety and efficacy
  – Strategies for cost/effectiveness optimization in the single patient:
    • Usage of lead in phase as a sensitivity and tolerability test
    • Usage of response predictors (IL28)
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Challenges to Categorizing Previous Therapy Response

• Challenges in clinic setting
  – Lack of detailed records
  – Lack of standardized definitions of response
  – Lack of patient evaluation at key time points on previous therapy
  – Potential lapses in patient memory

• Differentiation of previous partial response vs null response is unfeasible in some circumstances.

• What about pre treatment response?
RESPOND-2: SVR by Week 4
PR Lead-In Response

Poorly Responsive to IFN
<1 log_{10} viral load decline at treatment week 4

Responsive to IFN
≥1 log_{10} viral load decline at treatment week 4

Bacon R, et al. AASLD 2010
REALIZE (telaprevir): SVR by Week 4 response according to prior response category (LI T12PR48 arm)

<1 log_{10} HCV RNA reduction after 4-week Peg-IFN/RBV lead-in phase

- Prior relapsers: 10% (95% CI 36–88%)
- Prior partial responders: 40% (95% CI 23–89%)
- Prior null responders: 59% (95% CI 4–26%)

≥1 log_{10} HCV RNA reduction after 4-week Peg-IFN/RBV lead-in phase

- Prior relapsers: 94% (95% CI 90–98%)
- Prior partial responders: 59% (95% CI 41–77%)
- Prior null responders: 54% (95% CI 36–72%)

n/N= 8/13, 10/18, 6/41, 106/113, 16/27, 15/28

Foster GR, et al. J Hepatol 2011;54(Suppl. 1):S3
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Practical dosing and administration considerations with triple therapy

- **7am**
  - **Breakfast**
  - Protease inhibitor
  - Ribavirin

- **3pm**
  - *or*
  - Protease inhibitor
  - *or*

- **8pm**
  - *or*
  - Protease inhibitor
  - *or*

- **11pm**
  - *or*
  - Protease inhibitor
  - Ribavirin
Telaprevir bid vs Telaprevir tid

**OPTIMIZE STUDY:**
Primary endpoint: SVR12

- **SVR12 (%)**
  - T12(q8h)/PR: 270/371
  - T12(bid)/PR: 274/369

- T12(bid)/PR was non-inferior to T12(q8h)/PR for SVR12
  - Difference (95% CI): 1.5% (−4.9%, 12%)

Buti M et al AASLD 2013 Poster LB-8
Practical dosing and administration considerations with triple therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Meal</th>
<th>Drug</th>
<th>Meal</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-8 am</td>
<td>Breakfast</td>
<td>Protease inhibitor</td>
<td>Ribavirin</td>
<td></td>
</tr>
<tr>
<td>7 - 8pm</td>
<td>Dinner</td>
<td>Protease inhibitor</td>
<td>Ribavirin</td>
<td></td>
</tr>
</tbody>
</table>
## Drug-Drug Interactions Represent a Clinical Challenge*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC(^{[1]})</th>
<th>Contraindicated With TVR(^{[2]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoreceptor antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td><em>Hypericum perforatum</em> (St John’s wort)</td>
<td><em>Hypericum perforatum</em></td>
</tr>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
<td>Atorvastatin, lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drospirenone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension</td>
<td>Sildenafil or tadalafil when used for tx of pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Triazolam; orally administered midazolam</td>
<td>Orally administered midazolam, triazolam</td>
</tr>
</tbody>
</table>

*Studies of drug-drug interactions incomplete.

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Loss of Detectable (<20% of circulating virus) Resistance in Patients Stopping BOC or TVR + PegIFN/RBV

*Data from phase II studies.

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Boceprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with boceprevir-based therapy vs pegIFN/RBV alone

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Boceprevir + PegIFN/RBV</th>
<th>PegIFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>Treatment-experienced patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>44</td>
<td>11</td>
</tr>
</tbody>
</table>


ANEMIA MANAGEMENT:
- Ribavirin dose reduction
- EPO in cirrhotics?

NEUTROPENIA
- PEGIFN dose adjustment
- GCSF in cirrhotics?

DYSGEUSIA
- Specific food intake
Telaprevir-Related Adverse Events in Clinical Trials

- Most notable adverse events occurring more frequently with telaprevir-based therapy vs pegIFN/RBV alone:
  - Rash
  - Anemia
  - Anorectal symptoms

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage Telaprevir + PegIFN/RBV (n = 1797)</th>
<th>Percentage PegIFN/RBV (n = 493)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>56</td>
<td>34</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>Anorectal</td>
<td>29</td>
<td>7</td>
</tr>
</tbody>
</table>

ANEMIA MANAGEMENT:
- Ribavirin dose reduction
- EPO in cirrhotics?

RASH
- Rash management plan + topical steroids + antihistaminic

ANORECTAL DISCOMFORT
- Topical lidocaine preparations

New challenges of anti HCV therapy: key messages

- Complex schedules → computer assisted protocols or internal guidelines
- Costs → optimization of cost utility
- Adherence → bid for TVP
- Resistance: futility rules
- Side effects: PR dose adjustment, counselling, treatment and management plan
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Cirrhosis

• Rationale
  – SVR < 50% in HCV G1\(^1\)
  – Increased survival, lower decompensation rate and lower incidence of HCC after SVR\(^2\)

• Schedules
  – 12 PEG RBV TVP + 36 w PEG RBV\(^3\)
  – 4 PEG RBV + 44w PEG RBV BOC\(^4\)

3. Incivo SPC
## Cirrhosis: Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Naïve</th>
<th>Relapsers</th>
<th>Partial Responders</th>
<th>Null Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telaprevir</strong></td>
<td><strong>71% (F4)</strong></td>
<td><strong>84% (F4)</strong></td>
<td><strong>34% (F4)</strong></td>
<td><strong>14% (F4)</strong></td>
</tr>
<tr>
<td>Phase III Studies 1-3</td>
<td>59% (F3-F4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Boceprevir</strong></td>
<td><strong>42%</strong></td>
<td><strong>83% (F3-F4)</strong></td>
<td><strong>46% (F3-F4)</strong></td>
<td><strong>1/2</strong></td>
</tr>
<tr>
<td>Phase III Studies 4-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CUPIC</strong></td>
<td></td>
<td><strong>71% (SVR 12)</strong></td>
<td><strong>29% (SVR12)</strong></td>
<td></td>
</tr>
<tr>
<td>Telaprevir 7</td>
<td>_</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CUPIC</strong></td>
<td></td>
<td><strong>52% (SVR 12)</strong></td>
<td><strong>31% (SVR 12)</strong></td>
<td></td>
</tr>
<tr>
<td>Boceprevir 7</td>
<td>_</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Expanded Access TPV</strong></td>
<td><strong>85% (HCVRNA undetectable at 12 weeks)</strong></td>
<td><strong>85% (HCVRNA undetectable at 12 weeks)</strong></td>
<td><strong>77% (HCVRNA undetectable at 12 weeks)</strong></td>
<td><strong>68% (HCVRNA undetectable at 12 weeks)</strong></td>
</tr>
</tbody>
</table>

Efficacy and safety of boceprevir plus peginterferon–ribavirin in patients with HCV G1 infection and advanced fibrosis/cirrhosis

Savino Bruno¹,*, John M. Vierling², Rafael Esteban³, Lisa M. Nyberg⁴, Hugo Tanno⁵, Zachary Goodman⁶, Fred Poordad⁷, Bruce Bacon⁸, Keith Gottesdiener⁹, Lisa D. Pedicone¹⁰, Janice K. Albrecht¹¹, Clifford A. Brass¹², Seth Thompson¹³, Margaret H. Burroughs¹⁴

¹Department of Internal Medicine, A.O. Fatebenefratelli e Ospedale, Milan, Italy; ²Gastroenterology and Hepatology Section, Baylor College of Medicine, Houston, TX, United States; ³Internal Medicine and Liver Unit, Vall d’Hebron Hospital, Barcelona, Spain; ⁴Kaiser Permanente San Diego, CA, United States; ⁵Gastroenterology and Hepatology Service, Hospital Provincial del Centenario, Rosario, Argentina; ⁶Center for Liver Diseases, Inova Fairfax Hospital and the Betty and Guy Beatty Center for Integrated Research, Falls Church, VA, United States; ⁷Center for Liver Disease and Transplantation, Cedars-Sinai Medical Center, Los Angeles, CA, United States; ⁸Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis, MO, United States; ⁹Merck Sharp & Dohme Corp., Whitehouse Station, NJ, United States

Fig. 2. Sustained virologic response (SVR) by Metavir score in early responders (undetectable HCV RNA at week 8) vs. late responders (detectable HCV RNA at week 8).
Fig. 1. Sustained virologic response (SVR) in patients with advanced fibrosis/cirrhosis with (A) poor response vs. (B) good response to interferon.
## Cirrhosis: Safety

<table>
<thead>
<tr>
<th>Study</th>
<th>% SAE</th>
<th>% Severe Infections, Liver Decompensations, Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir Phase III Studies</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Boceprevir Phase III Studies</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>CUPIC Telaprevir</td>
<td>45% (at 16 w)</td>
<td>11.1% (at 16 w)</td>
</tr>
<tr>
<td>CUPIC Boceprevir</td>
<td>33% (at 16 w)</td>
<td>5.9% (at 16 w)</td>
</tr>
<tr>
<td>Telaprevir EAP</td>
<td>14%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

CUPIC: Risk of occurrence of death or severe complications

<table>
<thead>
<tr>
<th>Factors</th>
<th>Platelet count &gt; 100.000</th>
<th>Platelet Count &lt; 100.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin &gt; 3.5 g/dL</td>
<td>3.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>7.1%</td>
<td>40.6%</td>
</tr>
</tbody>
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Special Populations: HIV+

- Liver diseases (cirrhosis + HCC) 1st cause of death in HIV+\(^1\)
- HCV associated with renal and bone comorbidities\(^2-3\)
- SVR to anti HCV Tx associated with increased survival\(^4\)
- SVR in HCV G1 < 50%\(^5\)
- HCV G1 > 50% of HIV/HCV coinfected\(^6\)

Telaprevir and boceprevir Phase II trials in G1 HCV/HIV1 co-infected treatment naïves

<table>
<thead>
<tr>
<th>Variable</th>
<th>Telaprevir Study</th>
<th>Boceprevir Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not on cART</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>CD4 &amp; HIVRNA</td>
<td>≥500 &amp; HIVRNA≤1000.000</td>
<td>≥200 &amp; HIVRNA ≤50 c/mL</td>
</tr>
<tr>
<td></td>
<td>&gt; 300 &amp; HIVRNA ≤ 50 c/mL</td>
<td></td>
</tr>
</tbody>
</table>

No new safety signal compared to mono-infected patients
Proportion of patients with advanced fibrosis (F3/F4 or S4/S6) in HIV/HCV coinfected patients enrolled in previous studies with PR and in DAA Phase 2 studies

* S5 and S6 only
TelapreVIH: P+R+ Telaprevir in HIV/HCV PR experienced
Week 16 (4 PR + 12 PRT) virologic response

Cotte L, et al. CROI 2013, Abstract 36
BocepreVIH: P+R+ Boceprevir in HIV/HCV PR experienced

**Week 16 (4 PR + 12 PRT) virologic response**

<table>
<thead>
<tr>
<th>Treatment response</th>
<th>Fibrosis stage</th>
<th>Anti-retroviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsers</td>
<td>F1</td>
<td>ATV/r RAL</td>
</tr>
<tr>
<td>vBT</td>
<td>F2</td>
<td>Other</td>
</tr>
<tr>
<td>Partial R.</td>
<td>F3</td>
<td></td>
</tr>
<tr>
<td>Null R.</td>
<td>F4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion of patients with HCV RNA &lt;15 IU/ml (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
</tbody>
</table>

Poizot-Martin I, et al. CROI 2013, Abstract 37
# Antiretroviral therapy in candidates for PEG IFN + RBV + TPV.

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Antiretrovirals</th>
<th>TELAPREVIR</th>
<th>BOCEPREVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>AZT, ddi, d4T</td>
<td>Avoid coadministration</td>
<td>Avoid Coadministration</td>
</tr>
<tr>
<td></td>
<td>ABC: No data</td>
<td>Combine with caution</td>
<td>Combine with caution</td>
</tr>
<tr>
<td></td>
<td>Potential interaction with UDP-glucuronyl tranferase</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF</td>
<td>Can be combined</td>
<td>Can be combined</td>
</tr>
<tr>
<td></td>
<td>FTC, LAM. No Data but no potential interactions</td>
<td>Can be combined</td>
<td>Can be combined</td>
</tr>
<tr>
<td>PI</td>
<td>LPV/R, DRV/R, FPV/R,</td>
<td>Avoid coadministration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATZ/R</td>
<td>Can be combined</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV</td>
<td>1125 mg tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>Avoid coadministration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>Can be Combined</td>
<td>Can be combined ?</td>
</tr>
<tr>
<td></td>
<td>ETV</td>
<td>Can be combined</td>
<td>Combine with caution§</td>
</tr>
<tr>
<td>II</td>
<td>RAL</td>
<td>Can be combined</td>
<td>Can be combined</td>
</tr>
</tbody>
</table>

^ Potential interaction with UDP-glucuronyl tranferase;  
* Rilpivirine AUC +79% → check QT  
§ Etravirine AUC - 23%: caution in patients with history of multiresistance
Boceprevir and Telaprevir in LT recipients:
Rationale

• Accelerated disease progression\(^1\)
• Low response to SOC in HCV G1\(^2\)

Background: telaprevir increases exposure to immunosuppressants (CYP3A4 & P-gp substrates)

<table>
<thead>
<tr>
<th>Calcineurin Inhibitor</th>
<th>$C_{\text{max}}$</th>
<th>AUC</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A</td>
<td>1.3-fold increase</td>
<td>4.6-fold increase</td>
<td>From 12 → 42 hours</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>9.4-fold increase</td>
<td>70-fold increase</td>
<td>From 41 → 196 hours</td>
</tr>
</tbody>
</table>

- Significant immunosuppressant dose reductions and prolongation of the dosing intervals will be required.
- Close monitoring of immunosuppressant blood levels, renal function and immunosuppressant related side effects are recommended when co-administered with telaprevir.
Background: boceprevir increases exposure to immunosuppressants (CYP3A4 & P-gp substrates)

- Boceprevir co-administration significantly increased blood concentrations of cyclosporine and tacrolimus
- Therapeutic medicine monitoring is recommended when administering boceprevir with CYP3A4/5 substrates that have a narrow therapeutic window (e.g., tacrolimus, cyclosporine)
- Individual patients may require additional titration of their immunosuppressant dosage when boceprevir is started or stopped to ensure clinically effective blood levels

<table>
<thead>
<tr>
<th>Calcineurin Inhibitor</th>
<th>Cmax</th>
<th>AUC</th>
<th>t1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A</td>
<td>2-fold increase</td>
<td>2.6-fold increase</td>
<td>From 11.3 → 15.7 hours</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>10-fold increase</td>
<td>17-fold increase</td>
<td>From 36.7 → 61.3 hours</td>
</tr>
</tbody>
</table>

Hulskotte EGJ, et al. Global Antivir J 2011;7(Suppl. 1):110; Boceprevir EU SmPC
Triple Therapy post LT

• Pooled analysis 8 AASLD abstracts 1 paper
• 204 post LTx patients – Triple treatment
  – 81% Telaprevir
  – 19% Boceprevir
• Disease stage & previous treatment
  – > 50% with F3-F4 or FCH
  – > 50% experienced
• Immunosuppression:
  – Cya 62%
  – Tac 32%
  – Syrolimus 6%
• 48 weeks of therapy

Burton J et al. AASLD 2012 #211, Pungpapong S et al. AASLD 2012 #10; Coilly A et al AASLD 2012 #9; Aqel B et al AASLD 2012 # 706; Mantry PS et al. AASLD 2012, # 712; Koning L et al. AASLD 2012 #209; Nar S et al AASLD 2012 #720; Kuo PY et al. AASLD 2012 #719; Werner CR et al Liver Transpl 2012
Triple therapy post LT

- 30% stopped
- 2/3 Futility
- 1/3 AE
- 3% Death

Burton J et al. AASLD 2012 #211, Pungpapong S et al. AASLD 2012 #10; Coilly A et al AASLD 2012 #9; Aqel B et al AASLD 2012 #706; Mantry PS et al. AASLD 2012, #712; Koning L et al. AASLD 2012 #209; Nar S et al AASLD 2012 #720; Kuo PY et al. AASLD 2012 #719; Werner CR et al Liver Transpl 2012
Triple therapy post LT – Safety & Drug Drug interactions

• Anemia
  – Lower Ribavirin starting dose
  – 90% of patients required growth factors
  – Transfusion are common
• Use Lead In regardless of PI in most of the studies
  – Assess Tolerability
  – Adjust PEG IFN & RBV dose
  – Minimize risk of PI discontinuation
• DDI with CNI and mTOR-I change over time
• Stop or switch or non essential medications
<table>
<thead>
<tr>
<th>Population</th>
<th>Cirrhotics</th>
<th>HIV+</th>
<th>LT recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>Maximal cost effectiveness due to higher morbidity and mortality in the short term. SVR → increased survival but &lt; 50% in HCV G1</td>
<td>HCV Main cause of Death. SVR → increased survival. Rapid progression. Associated with comorbidities. Poor response to SOC in HCV G1</td>
<td>Rapid progression. Poor response to SOC in HCV G1</td>
</tr>
<tr>
<td>Schedule</td>
<td>Extended treatm. duration</td>
<td>Extended treatm. duration</td>
<td>Extended treatment duration. Lead in used in most series</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Lower Stopping rules and Lead in to maximize cost eff.</td>
<td>Similar to HIV-</td>
<td>Lower</td>
</tr>
<tr>
<td>Safety</td>
<td>Worse: caution with Albumin &lt; 4 and/or PLT&lt; 100.000</td>
<td>Similar to HIV-</td>
<td>Worse</td>
</tr>
<tr>
<td>Challenges</td>
<td>Safety: Infections and decompensation</td>
<td>Few data in easy to treat pts. Limitation of concurrent cART regimen</td>
<td>Interaction with CNI no data on mTOR I. Infections and decompensation</td>
</tr>
</tbody>
</table>