Drug-drug Interactions in Hepatitis C Therapy

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Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
A very recent case…..

- ♂, 46y, HCV genotype 1b, DM II, liver cirrhosis, EtOH abuse in past
- Start of DAA therapy incl. telaprevir, on Feb 13, 2012
- Admitted in hospital on March 14, 2012 feeling very sick.
- Lab results: CK 34,010 (normal: < 170); LD 1,438 (normal: <250); ASAT 882 (normal: <35); creatinine 67
A very recent case.....

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• Admitted in hospital on March 14, 2012 feeling very sick.
• Lab results: CK 34,010 (normal: < 170); LD 1,438 (normal: <250); ASAT 882 (normal: <35); creatinine 67

  **Rhabdomyolysis!**

• Patient was also treated by cardiologist with simvastatin 80mg BID
• TVR inhibits CYP3A-mediated metabolism of simvastatin = contra-indication
Outline

• Summary of Ribavirin & IFN-α

• Description of PK profiles of HCV PI therapies

• Interpretation of interpatient PK variability & PK/PD relationships

• Review of drug-drug interactions, based on:
  • Clinical data
  • Theoretical assumptions

• Conclusions
Ribavirin (RBV) & IFN-α

- RBV: contra-indicated with other myelotoxic agents (ZDV, ganciclovir, etc.)

- RBV: contra-indicated with DDI, d4T because of mitochondrial toxicity

- RBV – abacavir: conflicting results
  - Hypothesis: competition for intracellular phosphorylation → reduced HCV response?
  - Data originate from era when lower doses of RBV were used
  - Avoid abacavir if possible

- IFN-α: small increase in methadone levels (??)
Telaprevir pharmacokinetics (1)

- Limited information in peer-reviewed literature

- Absorption is improved with intake of food:
  - Low-fat (3.6g): +117%
  - Standard-fat (21g): +237%
  - High-fat (56g): +330%

- Recommendation in phase III trials: at least 20g of fat
Telaprevir pharmacokinetics (2)

• Distribution:
  • Protein binding: 59-76%
  • Alpha 1-acid glycoprotein & albumin
  • Apparent volume of distribution 252 L (CV: 72%)
  • Liver-plasma ratio 35:1 (rats; assuming density of liver is 1.0 g/mL; Perni et al. AAC 2006)
Telaprevir pharmacokinetics (3)

- **Metabolism:**
  - CYP3A4 substrate (+ non-CYP mediated metabolism)
  - CYP3A4 inhibitor

- **Elimination:**
  - Substrate & inhibitor of P-gp
  - Apparent oral CL: 32.4 L/h (CV 27%)
  - $T_{1/2}$: 9-11h at steady-state
  - Fraction excreted in urine: 1% (TVR and/or metabolites)
  - AUC in moderate hepatic impairment (CP-B):-46% (?)

Incivek Prescribing Information 2011
Boceprevir pharmacokinetics (1)

- Limited information in peer-reviewed literature

- Absorption is improved with intake of food: +65%
  - Not dependent on amount of fat
  - Not dependent on timing (before, during, after)

- Recommendation in phase III trials: with food

Victrelis Prescribing Information 2011
Boceprevir pharmacokinetics (2)

- **Distribution:**
  - Apparent volume of distribution: 772L
  - Protein binding: 75%

- **Metabolism:**
  - Primarily through aldo-ketoreductase (AKR = non-CYP)
  - Lesser extent through CYP3A4
  - BOC = CYP3A inhibitor
Boceprevir pharmacokinetics (3)

- **Elimination:**
  - Apparent oral CL: 161 L/h
  - $T_{1/2}$: 3.4h
  - Fraction excreted unchanged: 3%
  - AUC in hepatic impairment (CP 5-12): +32-45%; no dose adjustment
  - *In vitro*, BOC is not a substrate of OATP1B1, but at high doses a weak inhibitor

Victrelis Prescribing Information 2011
Chu et al. AASLD 2011; poster #378
# Boceprevir *in vitro* potential for interactions

**Table 1. *In vitro* evaluation of BOC as an inhibitor of major CYP and UGT enzymes in human liver microsomes**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>CYP/UGT Reaction</th>
<th>Direct inhibition</th>
<th>Time-dependent inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IC₅₀ (µM)</td>
<td>Maximum inhibition at 100 µM (%)</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Phenacetin O-deethylation</td>
<td>&gt;100</td>
<td>22</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin 7-hydroxylation</td>
<td>&gt;100</td>
<td>20</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Bupropion hydroxylation</td>
<td>&gt;100</td>
<td>2.3</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Amodiaquine N-dealkylation</td>
<td>&gt;100</td>
<td>25</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Diclofenac 4’-hydroxylation</td>
<td>&gt;100</td>
<td>3.6</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>S-Mephenytoin 4’-hydroxylation</td>
<td>&gt;100</td>
<td>25</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Dextromethorphan O-demethylation</td>
<td>&gt;100</td>
<td>45</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorzoxazone 6-hydroxylation</td>
<td>&gt;100</td>
<td>NA</td>
</tr>
<tr>
<td>CYP3A4/5</td>
<td>Testosterone 6β-hydroxylation</td>
<td>&gt;100</td>
<td>41</td>
</tr>
<tr>
<td>CYP3A4/5</td>
<td>Midazolam 1’-hydroxylation</td>
<td>11</td>
<td>91</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Estradiol 3-glucuronidation</td>
<td>&gt;100</td>
<td>40</td>
</tr>
<tr>
<td>UGT2B7</td>
<td>3’-azido-3’-deoxythymidine (AZT) glucuronidation</td>
<td>&gt;100</td>
<td>10</td>
</tr>
</tbody>
</table>

Chu et al. AASLD 2011; poster #378

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Telaprevir & boceprevir are CYP3A substrates: boosting by ritonavir?

Figure 1. Pharmacokinetic enhancement of VX-950 and SCH 503034 in rats

Closed symbols: oral dosing (5 mg/kg) alone; open symbols: oral co-dosing with ritonavir (5 mg/kg each); triangles: VX-950; circles: SCH 503034. Values represent mean (± SEM).


Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (1)

- Telaprevir phase 1B study (Reesink et al. Gastroenterol 2006)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean C_min (mg/L)</th>
<th>HCV-RNA decline in 14days</th>
</tr>
</thead>
<tbody>
<tr>
<td>450mg q8h</td>
<td>0.781</td>
<td>≥ 3 log_{10}</td>
</tr>
<tr>
<td>750mg q8h</td>
<td>1.054</td>
<td>≥ 4 log_{10}</td>
</tr>
<tr>
<td>1250mg q12h</td>
<td>0.676</td>
<td>≥ 3 log_{10}</td>
</tr>
</tbody>
</table>
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (2)

Incivek, clinical pharmacology review
Available at www.fda.gov
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (3)

Figure 3  Relationship Between Boceprevir $C_{\text{trough}}$ at Week 5 and Early Responsiveness to Combination Treatment With Boceprevir and Peginterferon alfa-2b (log HCV RNA change from baseline at Week 5).

Analysis of the data shows a clear relationship where a higher concentration of SCH 503034 at Week 5 is associated with a greater reduction in HCV RNA levels. This suggests that monitoring SCH 503034 levels can help predict treatment efficacy.

Source: Sponsor's study-report-phase-1-2-pk-pd.pdf, page 18

VICTRELIS, clinical pharmacology review
Available at www.fda.gov

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (4)

## Association of Boceprevir and Ribavirin PK with Occurrence of SVR or Anemia

<table>
<thead>
<tr>
<th>Event</th>
<th>Dataset</th>
<th>n/N</th>
<th>BOC PK Parameter</th>
<th>Boceprevir PK</th>
<th>Ribavirin AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p-Value</td>
</tr>
<tr>
<td>SVR</td>
<td>BOC arms only</td>
<td>136/197</td>
<td>AUC</td>
<td>0.989 (0.691, 1.415)</td>
<td>0.9501</td>
</tr>
<tr>
<td>SVR</td>
<td>All arms</td>
<td>160/277</td>
<td>AUC</td>
<td>1.598 (1.315, 1.941)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SVR</td>
<td>All arms</td>
<td>163/291</td>
<td>Presence</td>
<td>4.372 (2.478, 7.714)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Anemia</td>
<td>BOC arms only</td>
<td>106/197</td>
<td>AUC</td>
<td>1.058 (0.741, 1.513)</td>
<td>0.7552</td>
</tr>
<tr>
<td>Anemia</td>
<td>All arms</td>
<td>132/277</td>
<td>AUC</td>
<td>1.286 (1.061, 1.559)</td>
<td>0.0103</td>
</tr>
<tr>
<td>Anemia</td>
<td>All arms</td>
<td>139/291</td>
<td>Presence</td>
<td>2.328 (1.292, 4.197)</td>
<td>0.0049</td>
</tr>
</tbody>
</table>

Stone et al. AASLD 2011; poster #1342
Summary of PK/PD relationships

• Dose-finding studies indicate $C_{\text{min}}$ is most important PK parameter to predict response

• The “average patient” will have DAA exposure on the maximum plateau but how much of the failures is explained by PK?

• Phase III studies exclude patients with potential negative effect on DAA exposure

• Generally, interpatient variability in PK in clinical practice is larger than in phase III studies (food, co-medication, adherence)

• Therapeutic range for DAAs currently unknown
Overview of drug-drug interaction studies  
(published or presented)

1. Effect of telaprevir on PK of other drugs

2. Effect of other drugs on telaprevir PK

3. Effect of boceprevir on PK of other drugs

4. Effect of other drugs on boceprevir PK
Telaprevir and immunosuppressants

Fig. 1. Dose-normalized mean (SD) blood concentration-time profiles of cyclosporine following administration of cyclosporine alone and with telaprevir (log-linear scale).

AUC: 4.1 fold ↑

Fig. 2. Dose-normalized mean (SD) blood concentration-time profiles of tacrolimus following administration of tacrolimus alone and with telaprevir (log-linear scale).

AUC: 70.3 fold ↑

Garg et al. Hepatology 2011

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona
Telaprevir and other CYP3A substrates: amloidipine

AUC: 2.79 fold ↑

 Recommendation: caution

Lee et al. AAC 2011

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona

FIG. 1. Mean plasma concentration-time profile of amlodipine following oral administration with and without telaprevir. Error bars represent the standard error of the mean.

FIG. 2. Mean plasma concentration-time profile of atorvastatin following oral administration with and without telaprevir. Error bars represent the standard error of the mean.

AUC: 7.88 fold ↑

contra-indication
Telaprevir and oral contraceptives

AUC: -28%

Recommendation: use alternative non-hormonal methods

AUC: -11%
Telaprevir and methadone

AUC: -29%

Recommendation: clinical monitoring as the dose of methadone may need to be adjusted
Variable effect of telaprevir on HIV PI exposure

Presented at the 10th Eu Meeting on HIV & Hepatitis, 28-30 March 2012, Barcelona

### Effect of telaprevir on PK of HIV medications

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on AUC</th>
<th>Effect on C&lt;sub&gt;min&lt;/sub&gt;</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>-7%</td>
<td>-2%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>ATV/r</td>
<td>+17%</td>
<td>+85%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-40%</td>
<td>-42%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>FPV/r</td>
<td>-47%</td>
<td>-56%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>LPV/r</td>
<td>+6%</td>
<td>+14%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>RAL</td>
<td>+31%</td>
<td>+78%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2011</td>
</tr>
<tr>
<td>TDF</td>
<td>+30%</td>
<td>+41%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2008</td>
</tr>
</tbody>
</table>

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## Effect of other medications (non-HIV) on telaprevir PK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on AUC</th>
<th>Effect on $C_{\text{min}}$</th>
<th>Can be used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>-7%</td>
<td>-9%</td>
<td>Yes</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>-2%</td>
<td>ND</td>
<td>Yes</td>
</tr>
<tr>
<td>Ketoconazole (KCZ)</td>
<td>+62%</td>
<td>ND</td>
<td>$\leq 200\text{mg KCZ/day}$</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>-1%</td>
<td>0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Rifampin</td>
<td>-92%</td>
<td>ND</td>
<td>No</td>
</tr>
</tbody>
</table>

ND = not determined
### Effect of HIV medications on telaprevir PK

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>TVR dose</th>
<th>Effect on TVR AUC</th>
<th>Effect on TVR C&lt;sub&gt;min&lt;/sub&gt;</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>750mg q8h</td>
<td>-26%</td>
<td>-47%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>EFV</td>
<td>1125mg q8h</td>
<td>-18%</td>
<td>-25%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>ATV/r</td>
<td>750mg q8h</td>
<td>-20%</td>
<td>-15%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>DRV/r</td>
<td>750mg q8h</td>
<td>-35%</td>
<td>-32%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>FPV/r</td>
<td>750mg q8h</td>
<td>-32%</td>
<td>-30%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>LPV/r</td>
<td>750mg q8h</td>
<td>-54%</td>
<td>-52%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>RAL</td>
<td>750mg q8h</td>
<td>+7%</td>
<td>+14%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2011</td>
</tr>
<tr>
<td>TDF</td>
<td>750mg q8h</td>
<td>0%</td>
<td>+3%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2008</td>
</tr>
</tbody>
</table>

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Boceprevir and immunosuppressants

Tacrolimus AUC: 17.0 fold ↑

Cyclosporine AUC: 2.6 fold ↑

Hulskotte et al. 16th Hep-DART, 2011
Boceprevir and statins

Atorvastatin AUC: 2.3 fold ↑

Pravastatin AUC: 1.5 fold ↑

Hulskotte et al. 16th Hep-DART, 2011
### Effect of boceprevir on PK of HIV medications

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on AUC</th>
<th>Effect on $C_{\text{min}}$</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>+5%</td>
<td>ND</td>
<td>Yes</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>EFV</td>
<td>+20%</td>
<td>ND</td>
<td>No</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>ATV/r</td>
<td>-35%</td>
<td>-49%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>LPV/r</td>
<td>-34%</td>
<td>-43%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-44%</td>
<td>-59%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>RAL</td>
<td>+1%</td>
<td>ND</td>
<td>Yes</td>
<td>De Kanter et al. CROI 2012</td>
</tr>
</tbody>
</table>

ND = not determined

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# Effect of HIV medications on boceprevir PK

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on BOC AUC</th>
<th>Effect on BOC $C_{min}$</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>+8%</td>
<td>+8%</td>
<td>Yes</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>EFV</td>
<td>-19%</td>
<td>-44%</td>
<td>No</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>ATV/r</td>
<td>-5%</td>
<td>-18%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>LPV/r</td>
<td>-34%</td>
<td>-43%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-32%</td>
<td>-35%</td>
<td>No</td>
<td>Hulskotte et al. CROI 2012</td>
</tr>
<tr>
<td>RAL*</td>
<td>+7%</td>
<td>ND</td>
<td>Yes</td>
<td>De Kanter et al. CROI 2012</td>
</tr>
</tbody>
</table>

* vs. historical controls
ND = not determined
Some comments on DAA – ARV interaction data and label recommendations

• Telaprevir:
  • EFV (with dose adjustment of TVR), ATV/r and RAL are allowed in TVR studies in HCV/HIV co-infected studies
  • Increase renal function monitoring if patient is on TDF
  • Phase II studies: short-term data in small numbers of patients
  • If possible, avoidance of drug-drug interaction is preferred (raltegravir)

• Boceprevir:
  • With EFV: $C_{\text{min}}$ levels of BOC were decreased by 44% = contra-indication while for TVR an increased dose of 1125mg q8h led to 25% decrease = allowed
  • Phase II studies: short-term data in small numbers of patients
  • Only reasonable option: Truvada + RAL
Be careful when looking at phase II study data....

### SVR-12 by ARV Regimen on Day 1

<table>
<thead>
<tr>
<th>ARV Regimen</th>
<th>PR (N=34)</th>
<th>B/PR (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>8/13 (62%)</td>
<td>12/18† (67%)</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>0/10 (0%)</td>
<td>10/15‡‡ (67%)</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>0/5 (0%)</td>
<td>8/12 (67%)</td>
</tr>
<tr>
<td>Other PI/r*</td>
<td>0/3 (0%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Raltegravir**</td>
<td>1/3 (33%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Other††</td>
<td>0</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

†Excludes 2 patients not yet at FW12 but undetectable at FW4 and ‡‡ 1 not yet at FW12 but undetectable at FW4.

*Includes saquinavir, fosamprenavir and tipranavir

**Raltegravir without concurrent HIV PI/r

††Other ARVs were maraviroc and efavirenz

Sulkowski et al. CROI 2012
Examples contra-indicated drugs and cautions

- Rifampin, rifabutin and other enzyme inducers (anti-epileptics, St John’s wort)
- Alfuzosin
- Ergot derivatives
- Atorvastatin, simvastatin
- Pimozide
- Sildenafil, tadalafil
- Midazolam, triazolam
- Calcium channel blockers (other than amlodipine)
- Corticosteroids (systemic and inhaled/nasal)
- Azole antifungal agents
- Antiarrhythmics, digoxin
- Colchicine
- Methadone
Conclusions

- Drug-drug interactions with DAAs are here to stay
- TVR may be more problematic than BOC with non-HIV medications
- TVR easier to be combined with HIV medications than BOC

- Rapidly evolving field: make sure you are updated by:
  - Check www.hep-druginteractions.org
  - Consult a clinical pharmacologist/pharmacist
  - Read a review, e.g., Seden & Back: DAAs for hepatitis C and ARVs; potential for drug-drug interactions. Curr Opinion HIV AIDS 2011;6; 514-26
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