Clinical Pharmacology of DAA’s for HCV: What’s New & What’s In Pipeline

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Janssen R&D Activities For Telaprevir

• Phase 3 Studies:
  • C211/OPTIMIZE: q8hr vs BID
  • C3008/INSIGHT: HIV-HCV
  • C3006/REPLACE: Hepatic Transplant

• Phase 1 Studies:
  • HPC1001: Hepatic Impairment
  • HPC1002: DDI Anti-Epileptic Agents
Key Clinical Pharmacology Characteristics

Distribution & Elimination

- Typical apparent volume of distribution (Vd) was estimated to be 252 (L)
- 59–76% protein binding in human plasma (albumin and AAG)
- Elimination predominantly via feces, with minimal excretion into urine
- Apparent elimination half-life about 4 hours after single-dose administration, but effective half-life of 9–11 hours at steady-state

Metabolism

- Metabolism by CYP3A4, substrate of P-glycoprotein (P-gp)
- Extensive metabolism (hydrolysis, oxidation, reduction)
  - Non-CYP mediated metabolism
  - Inter-conversion to inactive isomer
- Telaprevir is a potent, time-dependent inhibitor of CYP3A4, and can inhibit/saturate intestinal P-g
- On going in vitro assessments
- In vitro studies inconsistent with CYP induction, although “cannot be excluded”.

**TVR & Food Effect**

- **Dosing Recommendation:**
  - TVR (750 mg, Q8h) to be dosed with food which is not low in fat

- **Compared to standard meal (21 g fat, 533 kcal):**
  - High Fat: ↑ 20% (56g fat, 928 kcal)
  - Low Calorie/High Protein: ↓ 26% (9 g fat, 260 kcal)
  - Low Calorie/Low Fat: ↓ 39% (3.6 g fat, 249 kcal)
  - Fasted: ↓ 73%

- **Standard meal used as reference throughout development**
Drug Metabolism: CYP3A

CYP3A is involved in the metabolism of majority of drugs.

CYP3A is the most abundant enzyme in the liver.

Telaprevir is metabolized by CYP3A and is a potent inhibitor of this enzyme.
Potential for increased exposure to CYP3A-substrates during combination with telaprevir
Active Drug Transporters

absorption

efflux
Effect of TVR on Digoxin

Digoxin AUC ↑ 2-fold: TVR is a Pgp inhibtor

Potential for increased exposure to Pgp-substrates during combination with telaprevir
**Effect of Co-Administered Agents on TVR**

- Increased exposure to telaprevir with CYP3A inhibition (after single-dose)
- Reduced exposure to TVR with CYP3A induction

**Agents and Their Effects**
- ketoconazole (400 mg)
- fAPV/r
- Tenofovir DF
- Ritonavir (SD)
- Ritonavir (MD)
- Rifampin
- Oral contraceptive
- LPV/r
- Esomeprazole
- Escitalopram
- Efavirenz
- DRV/r
- ATV/r

**Graphically Represented Data**
- AUC ↓
- AUC ↑
- LSMratio (90% CI)
Effect of TVR on Co-Administered Agents

- Potential for increased exposure to CYP3A4 substrates with TVR.
Drug Metabolism & Transport

- **Substrate Interaction**
  - Limited AUC
  - Limited Penetration

- **Inhibitor Interaction**
  - Enhanced AUC
  - Enhanced Penetration

- **Inducer Interaction**
  - Limited AUC
  - Limited Penetration
Effect of Low Dose Ritonavir on TVR?

Mean (SE) TVR PK Profiles

2-fold increase with RTV on Day 1

Highest exposure with TVR 750 mg q8h

25-30% lower with RTV on Day 14 (q12h)

### Other Examples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Drug</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>escitalopram*</td>
<td>↔ telaprevir</td>
<td>Clinical relevance unknown. Doses may need to be increased when combined with telaprevir.</td>
</tr>
<tr>
<td></td>
<td>↓ escitalopram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC 0.65 (0.60-0.70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{\text{max}} 0.70 (0.65-0.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{\text{min}} 0.58 (0.52-0.64)</td>
<td>mechanism unknown</td>
</tr>
<tr>
<td>ethinylestradiol*</td>
<td>↓ ethinylestradiol</td>
<td>Additional methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir. Patients using oestrogens as hormone replacement therapy should be clinically monitored for signs of oestrogen deficiency. Refer to sections 4.4 and 4.6.</td>
</tr>
<tr>
<td>norethindrone*</td>
<td>↔ norethindrone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC 0.89 (0.86-0.93)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{\text{max}} 0.85 (0.81-0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{\text{min}} 0.94 (0.87-1.00)</td>
<td>mechanism unknown</td>
</tr>
<tr>
<td>zolpidem (non-benzodiazepine sedative)*</td>
<td>↓ zolpidem</td>
<td>Clinical relevance unknown. Increased dose of zolpidem may be required to maintain efficacy.</td>
</tr>
<tr>
<td></td>
<td>AUC 0.53 (0.45-0.64)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C_{\text{max}} 0.58 (0.52-0.66)</td>
<td>mechanism unknown</td>
</tr>
</tbody>
</table>
### Protein Displacement Interactions

#### Example: Single Drug

- **Total Drug Concentration:** 3
- **Free Concentration:** 1
- **Free Fraction:** 33%

**PK**

*Initial↑ in free concentrations are subject to systemic clearance*

**Key Message**

Free concentrations are responsible pharmacologic activity (PD), and are subject to systemic clearance (PK)

#### Example: Two Drugs

- **Total Drug Concentration:** 2
- **Free Concentration:** 1
- **Free Fraction:** 50%

**Displacement Trend:**

- ↓ Total concentration
- ≈ Free concentration
- ↑Free Fraction

**LIMITED CLINICAL IMPACT**

#### Telaprevir Appears To Be Subject To Some Protein Displacement Interactions

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*Image and text content related to protein displacement interactions.*
Effect of TVR on Methadone

C135 Study

30% Reduction in R-Methadone

Mechanistic Explanation?:

Methadone is a Substrate of CYP3A4

TVR is an Inhibitor Of CYP 3A4, But Not An Inducer of CYP3A4

Consider Protein Displacement

Van Heeswijck, R. et al, EASL, 2011
Effect of TVR on Methadone

- Total R-Methadone Reduced by -31%....
- ...But Free R-Methadone Concentration Maintained With No Impact on Drug Craving

**NARCOTIC ANALGESIC**

<table>
<thead>
<tr>
<th>methadone*</th>
<th>↓ R-methadone</th>
<th>AUC 0.71 (0.66-0.76)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; 0.71 (0.66-0.76)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; 0.69 (0.64-0.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No effect on unbound R-methadone concentrations.</td>
<td>Displacement of methadone from plasma proteins.</td>
<td>No adjustment of methadone dose is required when initiating co-administration of telaprevir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. QT interval prolongation and Torsade de Pointes have been reported with methadone (see section 4.4). ECG should be monitored at baseline and regularly during telaprevir treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Drug Drug Interactions With ARV
Summary

- Based on current DDI data, TVR can be combined with:
  - Ritonavir-boosted atazanavir
  - Efavirenz (higher dose of TVR; 1125 mg q8h)
  - Tenofovir
  - Raltegravir
  - Rilpivirine
  - Etravirine
  - NRTIs (not studied, but no DDI expected)

- Protease Inhibitors: *in vitro* evaluation to determine mechanism of DDI is ongoing for Darunavir and other PI’s
## Effect of ARV on TVR

<table>
<thead>
<tr>
<th>ARV</th>
<th>Telaprevir Dose</th>
<th>Ratio of TVR PK With/Without ARV (Healthy Volunteer)</th>
<th>Ratio of TVR PK With/Without ARV (VX-08-950 110 Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>750 mg q8h</td>
<td>15% ↓</td>
<td>31% ↑ *</td>
</tr>
<tr>
<td>EFV</td>
<td>750 mg q8h</td>
<td>47% ↓</td>
<td>26% ↓</td>
</tr>
<tr>
<td>TDF + EFV</td>
<td>1125 mg q8h</td>
<td>25% ↓</td>
<td>18% ↓</td>
</tr>
<tr>
<td>TDF</td>
<td>750 mg q8h</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>RAL</td>
<td>750 mg q8h</td>
<td>14% ↑</td>
<td>↔</td>
</tr>
<tr>
<td>ETR</td>
<td>750 mg q8h</td>
<td>25% ↓</td>
<td>16% ↓</td>
</tr>
<tr>
<td>RPV</td>
<td>750 mg q8h</td>
<td>13% ↓</td>
<td>8% ↓</td>
</tr>
</tbody>
</table>

* ATV/r based ART regimens, interim data

** EFV based ART regimens, interim data
## Effect of TVR on ARVs

<table>
<thead>
<tr>
<th>ARV</th>
<th>Telaprevir Dose</th>
<th>Ratio of ARV PK With/Without TVR (Healthy Volunteer)</th>
<th>Ratio of ARV PK With/Without TVR (VX-08-950 110 Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;min&lt;/sub&gt;</td>
<td>AUC</td>
</tr>
<tr>
<td>ATV/r</td>
<td>750 mg q8h</td>
<td>85% ↑</td>
<td>17% ↑</td>
</tr>
<tr>
<td>EFV</td>
<td>750 mg q8h</td>
<td>↔</td>
<td>18% ↓</td>
</tr>
<tr>
<td>TDF + EFV</td>
<td>1125 mg q8h</td>
<td>17% ↑</td>
<td>↔</td>
</tr>
<tr>
<td>TDF</td>
<td>750 mg q8h</td>
<td>41% ↑</td>
<td>30% ↑</td>
</tr>
<tr>
<td>RAL</td>
<td>750 mg q8h</td>
<td>78% ↑</td>
<td>31% ↑</td>
</tr>
<tr>
<td>ETR</td>
<td>750 mg q8h</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>RPV</td>
<td>750 mg q8h</td>
<td>89% ↑</td>
<td>79% ↑</td>
</tr>
</tbody>
</table>

* ATV/r based ART regimens, interim data

** EFV based regimens, interim data
# TVR & HIV PI’s

<table>
<thead>
<tr>
<th>Co-Administered Drug</th>
<th>Co-Administered Drug</th>
<th>Dose/Regimen</th>
<th>Telaprevir</th>
<th>n</th>
<th>LSM Ratio (90% CI), Based on AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Administered Drug</td>
</tr>
<tr>
<td>Lopinavir (LPV/rtv)</td>
<td>400/100 mg bid</td>
<td>750 mg q8h</td>
<td>21</td>
<td>1.06</td>
<td>(0.96, 1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46</td>
<td>(0.41, .52)</td>
</tr>
<tr>
<td>Atazanavir (ATV/rtv)</td>
<td>300/100 mg qd</td>
<td>750 mg q8h</td>
<td>20</td>
<td>1.17</td>
<td>(0.97, 1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>(0.76, 0.85)</td>
</tr>
<tr>
<td>Darunavir (DRV/rtv)</td>
<td>600/100 mg bid</td>
<td>750 mg q8h</td>
<td>20</td>
<td>0.6</td>
<td>(0.57, 0.63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
<td>(0.61, 0.69)</td>
</tr>
<tr>
<td>Fosamprenavir (fAPV/rtv)</td>
<td>700/100 mg bid</td>
<td>750 mg q8h</td>
<td>20</td>
<td>0.53</td>
<td>(0.49, 0.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
<td>(0.63, 0.72)</td>
</tr>
</tbody>
</table>
## DRV Displacement Data

### In vitro & In-vivo Data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parameter</th>
<th>Without VX-950</th>
<th>With VX-950</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Methadone</td>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>139.2</td>
<td>93.47</td>
</tr>
<tr>
<td>Darunavir</td>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>2964</td>
<td>1794</td>
</tr>
<tr>
<td>R Methadone</td>
<td>% Unbound</td>
<td>8.71</td>
<td>12.4</td>
</tr>
<tr>
<td>Darunavir</td>
<td>% Unbound</td>
<td>9.25</td>
<td>15.2</td>
</tr>
<tr>
<td>R Methadone</td>
<td>$\text{Free } C_p$ (ng/ml)</td>
<td>12.12</td>
<td>11.59</td>
</tr>
<tr>
<td>Darunavir</td>
<td>$\text{Free } C_p$ (ng/ml)</td>
<td>274.2</td>
<td>272.7</td>
</tr>
</tbody>
</table>

### Trend

- ↓ Total Concentration
- ↑ Free Fraction
- ~ Free Concentration
## TVR Displacement Data

**In Vivo & In Vitro Data**

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{min}}$ (ng/ml) (Ref C124)</th>
<th>% Unbound</th>
<th>$C_p$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without DRV/rtv</td>
<td>1835</td>
<td>12.2</td>
<td>224</td>
</tr>
<tr>
<td>With DRV/rtv</td>
<td>1237</td>
<td>15.6</td>
<td>193</td>
</tr>
</tbody>
</table>

↓30% Reduction In Total TVR

≈ Free Concentrations

↑30% Increase in Free Fraction
Effect of TVR on Co-Administered Agents

Summation of *in vivo* and *in vitro* data consistent with plasma protein displacement between TVR and DRV

- Consistent with in vivo ~30 to 40% in total TVR and DRV exposures
- Predict free concentrations of both will be constant, but need clinical confirmation
3008 DRV Sub-Study

Enroll approx 20 subjects on QD DRV/r, must enroll in DRV sub-study to participate in main-study

DRV Sub-Study
  - Intensive PK Day 1 and Week 2
    - total/unbound concentrations
  - Ongoing monitoring of HCV/HIV RNA
  - Staggered Enrollment
    - Pause after 10 pts reach wk2
  - PK (Total/Unbound), HIV/HCV RNA, Safety
Questions