Pharmacokinetic Enhancement with Ritonavir: More Than It Seems?

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PK Boosting of HCV Protease Inhibitors

• PK boosting with ritonavir is a well-accepted strategy for optimizing the efficacy and safety of protease inhibitors in HIV therapy
  – Increased plasma trough levels contribute to enhanced antiviral activity
  – Lower doses (and lower Cmax) may provide better safety
• C\text{trough} correlated with antiviral activity
• Similar metabolic pathways for HCV and HIV PIs
  – Primary metabolism via CYP3A
  – Metabolism inhibited by ritonavir (\textit{in vitro} CYP3A \text{Ki} = 15 \text{nM})
Inhibition of the Metabolism of Telaprevir and Boceprevir by Ritonavir in Human Liver Microsomes

- Similar inhibition in both human and rat liver microsomes:

![Graphs showing % Remaining (HLM) over time for Telaprevir and Boceprevir with different concentrations of Ritonavir](image)

Pharmacokinetic Boosting of Telaprevir and Boceprevir by Co-dosing with Ritonavir in Rats

Mean (±SE) Plasma Concentrations in Rats (5 mg/kg oral dose)

PK Boosting of HCV Protease Inhibitors with Ritonavir: Some Interesting Questions Since 2006

• Does ritonavir boost HCV PIs in humans?
• Can both classes of HCV PIs (ketoamides and acylsulfonamides) be boosted?
• Does ritonavir boosting increase antiviral activity?
• What is the best PK predictor(s) of PD: $C_{\text{max}}$, AUC, $C_{\text{min}}$?
• What are the mechanisms of ritonavir PK boosting?
  – Inhibition of metabolism
  – Inhibition of transport
• Does ritonavir boosting change the liver:plasma ratio?
• What is the effect of ritonavir induction?
Structures of Danoprevir and Narlaprevir

Narlaprevir (SCH900518)
Ketoamide

Danoprevir (ITMN-191)
Acylsulfonamide
PK Boosting of Narlaprevir by Ritonavir in Humans

Mean Narlaprevir Concentration/Time Profiles Based on Daily or Twice Daily Dosing from NEXT-1*

Daily and twice daily dosing achieved by metabolic inhibition with ritonavir
*Generated using Sparse Sampling and Population PK Model (No Lead-in Arms)

Poordad et al, AASLD, 2009
PK Boosting of Danoprevir by Ritonavir in Humans

- Boosting: $C_{\text{max}} \uparrow 3$-fold, $\text{AUC} \uparrow 6$-fold, $C_{12h} \uparrow >50$-fold
- 100/100 mg BID vs. 900 mg BID: $C_{\text{max}} \downarrow 23$-fold, $\text{AUC} \downarrow 16$-fold

Haznadar et al, EASL, 2010; Gane et al, EASL, 2010
Antiviral Activity of Narlaprevir/Ritonavir

Undetectable* HCV-RNA by Treatment Week

Poordad et al, AASLD, 2009

*HCV RNA < 10 IU/mL (includes all patients that received at least one dose of NVR, excluding control)
**Antiviral Activity of Danoprevir/Ritonavir**

**Danoprevir/r + SOC regimens provide more robust virologic response than unboosted + SOC**

- Unboosted 900 mg BID (n=7)
- Boosted 100/100 mg BID (n=9)
- Boosted 200/100 mg QD (n=8)
- Boosted 200/100 mg BID (n=8)

**Day 15 HCV RNA <LLOQ or <LLOD (%)**

- LLOQ = lower limit of quantification by Roche TaqMan Assay <43 IU/mL (<25 IU/mL for NSHC-003)
- LLOD = lower limit of detection by Roche TaqMan Assay <15 IU/mL (<9.3 IU/mL for NSHC-003)


Gane et al, EASL, 2010
ABT-450: *in vitro* Antiviral Activity

<table>
<thead>
<tr>
<th></th>
<th>Replicon EC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genotype 1a</td>
</tr>
<tr>
<td></td>
<td>no human plasma</td>
</tr>
<tr>
<td>ABT-450</td>
<td>0.9</td>
</tr>
<tr>
<td>MK-7009</td>
<td>0.75</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>2.2</td>
</tr>
</tbody>
</table>

- ABT-450 is a new acylsulfonamide HCV protease inhibitor
- Metabolism of ABT-450 is primarily mediated through CYP3A4
## ABT-450: *in vitro* Antiviral Activity

<table>
<thead>
<tr>
<th></th>
<th>Estimated EC&lt;sub&gt;50&lt;/sub&gt; (40% Human Plasma, nM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a-H77</td>
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<tr>
<td></td>
<td>R155 K</td>
</tr>
<tr>
<td>ABT-450</td>
<td>370</td>
</tr>
<tr>
<td>MK-7009</td>
<td>5200</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>1600</td>
</tr>
</tbody>
</table>

*Estimated EC<sub>50</sub> (mutant, 40% HP) = EC<sub>50</sub> (mutant, transient replicon) X Fold EC<sub>50</sub> (stable replicon, 40% HP).
Metabolism and PK of ABT-450

<p>| Intrinsic Clearance (Liver Microsomes, µL/mg/min) |
|------------------------------------|------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Rat</th>
<th>Dog</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-450</td>
<td>31</td>
<td>50</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;23</td>
</tr>
</tbody>
</table>

**Pharmacokinetics of ABT-450 in Dogs**

**Plasma**

- IV; 2.5 mg/kg
- PO; 5 mg/kg
- PO; 5 mg/kg w/RTV 5 mg/kg

**Liver**

- Liver; 2 mg/kg + RTV 5 mg/kg
- Plasma; 2 mg/kg + RTV 5 mg/kg

Liver:plasma ratio = 7
Ritonavir Boosting of ABT-450 in Humans

Effect of 100 mg RTV:
- ABT-450 $t_{1/2}$ ↑ from ~2.5 to ~ 5 hours
- ABT-450 $C_{max}$ ↑ 28-fold
- ABT-450 AUC ↑ 48-fold
- $C_{24h}$ ↑ nearly 200-fold
- PK boosting allows for higher exposure and QD dosing

<table>
<thead>
<tr>
<th>Species</th>
<th>ABT-450</th>
<th>Ritonavir</th>
<th>$t_{1/2}$ (h)</th>
<th>$C_{max}$ ($\mu$g/mL)</th>
<th>AUC ($\mu$g*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>5 mg/kg</td>
<td>—</td>
<td>1.2</td>
<td>6.3</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>1.8</td>
<td>22.7</td>
<td>84.8</td>
</tr>
<tr>
<td>Human</td>
<td>300 mg</td>
<td>—</td>
<td>2.7</td>
<td>0.12</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>100 mg</td>
<td>4.6</td>
<td>3.4</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Menon et al, Hep DART, 2009
### PK Boosting of ABT-450 by Ritonavir

#### Mean ABT-450 PK Parameters (Day 14 w/RTV)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>50/100 BID</th>
<th>100/100 BID</th>
<th>200/100 QD</th>
<th>300/100 QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.07</td>
<td>0.37</td>
<td>1.5</td>
<td>7.3</td>
</tr>
<tr>
<td>AUC (µg·h/mL)</td>
<td>0.41</td>
<td>1.6</td>
<td>5.6</td>
<td>36</td>
</tr>
<tr>
<td>AUC/Dose</td>
<td>16.5</td>
<td>31.5</td>
<td>32.5</td>
<td>128</td>
</tr>
</tbody>
</table>

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**Menon et al, Hep DART, 2009, Bernstein et al, Hep DART, 2009**
Boosting of Metabolically Stable Protease Inhibitor (AE-741) by Ritonavir

<table>
<thead>
<tr>
<th>Species</th>
<th>$C_{\text{int}}$ *</th>
<th>$C_{\text{max}}$ *</th>
<th>$AUC$ #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>13.8</td>
<td>16.9</td>
<td>54.3</td>
</tr>
<tr>
<td>Dog</td>
<td>15.1</td>
<td>37.0</td>
<td>435</td>
</tr>
</tbody>
</table>

*µL/mg/min, **µg/mL, #µg h/mL, 

Plasma Levels after Oral Dosing in Dogs (3 mg/kg)
Potential PK Boosting Through Transporter Inhibition by Ritonavir

Ritonavir May Boost ABT-450 via P-gp Inhibition

- Efflux ratio (6.3) in Caco-2 cells indicates active transport of ABT-450
- Active efflux partially (but not completely) blocked by selective P-gp inhibitor LY335979
- Ritonavir has been reported to inhibit P-gp \textit{in vitro} (IC$_{50}$ 0.2 - 16 µM, multiple systems)*
  - However, little effect on BBB P-gp transport of SQV \textit{in vivo}**
- Most likely inhibition in intestine where local concentrations are high

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
 & ABT-450 Papp (1X10$^{-6}$ cm/s) & \\
\hline
 & No inhibitor & + LY335979 & \\
\hline
A-to-B & 10.1 & 18.6 & \\
B-to-A & 63.8 & 59.4 & \\
Efflux Ratio & 6.3 & 3.2 & \\
\hline
\end{tabular}
\caption{ABT-450 is a P-gp Substrate}
\end{table}

Ritonavir Does Not Affect the Liver:Plasma Ratio of ABT-450

Plasma and Liver Concentrations in Dogs

- Liver; 2 mg/kg
- Liver; 2 mg/kg + RTV
- Plasma; 2 mg/kg
- Plasma; 2 mg/kg + RTV

Plasma or Liver Conc. (µg/mL or µg/g)

Time (Hours Post Dose)

Mean = 7.0
Mean = 6.7
ABT-450 $C_{\text{trough}}$ vs. Time

Bernstein et al, Hep DART, 2009
Ritonavir Boosting of HCV PIs: Conclusions

• As in HIV therapy, PK boosting by ritonavir can be advantageous for HCV protease inhibitors
  – Less frequent dosing → greater convenience
  – Increased $C_{trough}$ → greater virologic response
  – Decreased $C_{max}$ and AUC → potential for lower toxicity
• Both classes of HCV protease inhibitors (ketoamide and acylsulfonamide) may be candidates for PK boosting
• The mechanism of PK boosting of HCV PIs appears more complex than simple CYP3A inhibition (more studies needed)
  – Intestinal transport → likely
  – Biliary transport → possible
  – Hepatic uptake → less likely
• HCV PIs may be affected by ritonavir even if they are metabolically stable
• The boosting effect of other CYP3A inhibitors on HCV PIs may be distinct from ritonavir and requires study
Acknowledgments

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- Rob Ralston (Merck/Schering)