Transporters: Role in Clinical Development of HCV Compounds

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Introduction

♦ Drug discovery and development is moving away from metabolic liabilities
  – Increasing importance and evaluation of the role of transporters in drug disposition

♦ Unique challenges for transporter-mediated DDIs
  – Bioavailability vs. systemic clearance vs. distribution
  – Tissue and membrane localization (plasma vs. tissue concentration)
  – Lack of specificity of probe substrates and inhibitors
  – Limited understanding of $f_t$ (similar to $f_m$ for metabolism)
    • Decreases predictability of DDI magnitude
    • Mechanistic extrapolation to other conmeds, regimens and drug combinations
Introduction

- The field is advancing, learning from approaches applied to metabolic DDIs
  - International Transporter Consortium (ITC) white papers
  - US FDA and EU EMA guidance
    - Primary transporters of interest
    - Criteria for evaluation as substrate or inhibitor
    - Study design considerations

**P-gp/BCRP Inhibitor**

- Bi-directional transport assay with a probe P-gp substrate (e.g., in Caco-2 or MDR1-overexpressing polarized epithelial cell lines)
- Net flux ratio of a probe substrate decreases with increasing concentrations of the investigational drug
- Determine K_i or IC_{50} of the inhibitor
- [I]_{IC_{50}} (or K_i) > 0.1
- An in vivo drug interaction study with a P-gp substrate such as digoxin is recommended.

**P-gp/BCRP Substrate**

- In bi-directional transporter assay (e.g., in Caco-2 or MDR1-overexpressing polarized epithelial cell lines) is the net flux ratio of an investigational drug ≥ 2?
- Net flux ratio ≥ 2:
  - Is efflux significantly inhibited by one or more P-gp inhibitors?  
    - Yes: Probably a P-gp Substrate
    - No: Other efflux transporters are responsible for observed data
  - Complete an assessment of nonclinical and clinical information to determine whether an in vivo DDI study is warranted?
- Net flux ratio < 2:
  - Poor or non-P-gp substrate
Evolution of DDI Assessments
Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

Single Agent DDI Studies (2-way; Victim – Perpetrator)

**ARVs**

**ARVs + HCV DAAs**

### Benefits
- Direct + specific information for conmeds
- May be best for sensitive substrates

### Limitations
- Extrapolation to other conmeds is limited based on the conmeds evaluated
- Extrapolation to multi-drug regimen may be limited

**Drug X + conmed**

Clinical use with conmed

Extrapolate to clinical use with other conmeds

?
Evolution of DDI Assessments
Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

<table>
<thead>
<tr>
<th>Regimen DDI</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X/Y/Z + conmed</td>
<td>• Direct + specific information for conmeds • Informs on regimen effects</td>
<td>• Extrapolation to other conmeds is limited based on the conmeds evaluated • Extrapolation to other regimens may be limited • Large studies ($ due to Bioanalytical)</td>
</tr>
</tbody>
</table>

- **Regimen DDI Studies** (>2-way; specific/applicable data to use)
- **Single Agent DDI Studies** (2-way; Victim – Perpetrator)

- **ARVs**
- **ARVs + HCV DAAs**
Evolution of DDI Assessments
Polypharmacy required for HIV and HCV have been central to and benefited from this evolution.

**Single Agent DDI Studies (2-way; Victim – Perpetrator)**

**Regimen DDI Studies (>2-way; specific/applicable data to use)**

**Single Agent Probe Studies (obviate need for DDI studies)**

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**Drug X**

**Extrapolate to clinical use with various conmeds**

**Mechanistic understanding of DDI potential in vivo**

**Benefits**
- Provides mechanistic understanding of DDI potential in vivo
- Fewer studies required to inform broad conmed recommendations
- Fewer “DDI” studies

**Limitations**
- Extrapolation to multi-drug regimens may be complex
Evolution of DDI Assessments

Polypharmacy required for HIV and HCV have been central to and benefited from this evolution

**Regimen DDI Studies (>2-way; specific/applicable data to use)**

**Single Agent Probe Studies (obviate need for DDI studies)**

**Regimen Probe/Cassette Studies (can evaluate many questions)**

**Benefits**
- Mechanistic understanding of DDI potential of the regimen in vivo
- Fewer studies required to inform broad conmed recommendations

**Limitations**
- Extrapolation to other multi-drug or single-agent regimens may be complex

**ARVs**

**ARVs + HCV DAAs**

**Single Agent DDI Studies (2-way; Victim – Perpetrator)**

**Regimen Probe/Cassette**

- Drug X/Y/Z + Probe(s)
- Clinical use with various conmeds
- Mechanistic understanding of regimen DDI potential *in vivo*
GSI HCV DAA Clin Pharm Approach to DDIs
Fit For Purpose

<table>
<thead>
<tr>
<th>Compound / [Development Program]</th>
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<tbody>
<tr>
<td>GS-9451/LDV/TGV</td>
</tr>
<tr>
<td>(NS3/4 PI, NS5A, NS5B non-nuc)</td>
</tr>
<tr>
<td>GS-9451: efflux/uptake/metabolism</td>
</tr>
<tr>
<td>LDV: P-gp/BCRP</td>
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<tr>
<td>TGV: P-gp</td>
</tr>
<tr>
<td>Intra-regimen DDI</td>
</tr>
<tr>
<td>SOF (NS5B Nuc)</td>
</tr>
<tr>
<td>P-gp/BCRP substrate</td>
</tr>
<tr>
<td>LDV (NS5A) [LDV/SOF]</td>
</tr>
<tr>
<td>P-gp/BCRP substrate/inhibitor</td>
</tr>
<tr>
<td>GS-5816 (pan-GT NS5A) [GS-5816/SOF]</td>
</tr>
<tr>
<td>P-gp/BCRP/OATP substrate/inhibitor</td>
</tr>
</tbody>
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Transporter DDI Profile:
Non-Clinical + Early Clinical

Approach to Transporter DDIs
Regimen Probes
- Digoxin
- Rosuvastatin
- Pravastatin
- Cyclosporine
- Verapamil
- Rifampin

Single Agent DDIs
- Cyclosporine
- Tacrolimus
- Methadone
- ARV regimens
- ARV single agents
- OCs

Single Agent DDIs
- ARV regimens
  - O Cs
  - [Applied to LDV/SOF Regimen]

Single Agent Probes
- Digoxin
- Rosuvastatin
- Pravastatin
- Cyclosporine
- Ketoconazole
- Rifampin
P-gp Mediated DDI: Informing Post-Transplant Single Agent + Probe (high dose CsA) DDIs

CsA/Tac–SOF DDI Study

- Regimens
  - CsA: 600 mg single dose
  - Tac: 5 mg single dose
- To inform conmed restrictions in post-transplant setting
- Test “worst-case” scenario for transporter inhibition (P-gp/BCRP)

PK Results

<table>
<thead>
<tr>
<th>Object</th>
<th>Perpetrator</th>
<th>AUC</th>
<th>C_{max}</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF</td>
<td>CsA</td>
<td>↑353%</td>
<td>↑154%</td>
</tr>
<tr>
<td></td>
<td>Tac</td>
<td>↑13%</td>
<td>↓4%</td>
</tr>
<tr>
<td>GS-331007</td>
<td>CsA</td>
<td>↔</td>
<td>↓40%</td>
</tr>
<tr>
<td></td>
<td>Tac</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>SOF</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>SOF</td>
<td>↑9%</td>
<td>↓27%</td>
</tr>
</tbody>
</table>

- CsA and TAC can be administered with SOF without SOF dose adjustment

Post-Transplant Phase 2

- Recurrent HCV post-liver transplant (n=40)
- 24 weeks of SOF + RBV

PK Results

- Subjects on CsA (n=10) vs non-CsA (N=30) containing immunosuppressant regimens had similar SOF (↑15%) and GS-331007 (↔) AUC_{tau}
- No clinically significant differences in SOF or GS-331007 PK compared with historical data
  - ~2-fold higher GS-331007 AUC_{tau}; decreased renal function in post-transplant setting

P-gp–Mediated DDI:
Informing HIV/HCV Co-infection
Regimen + Single Agent DDIs

ARVs: Atripla (ATR), DRV/r, RAL, RPV

To support ARV-DAA combinations in HIV/HCV co-infection

<table>
<thead>
<tr>
<th>% Change in PK Parameter</th>
<th>Perpetrator</th>
<th>AUC</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
<th>C&lt;sub&gt;tau&lt;/sub&gt;</th>
</tr>
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<tbody>
<tr>
<td>SOF</td>
<td>ATR</td>
<td>↔</td>
<td>↓ 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>↑34%</td>
<td>↑ 45%</td>
<td></td>
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<tr>
<td></td>
<td>RAL</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPV</td>
<td>↔</td>
<td>↑ 21%</td>
<td></td>
</tr>
<tr>
<td>GS-331007</td>
<td>ATR</td>
<td>↔</td>
<td>↓ 23%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>DRV/r</td>
<td>↔</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td></td>
<td>RPV</td>
<td>↔</td>
<td></td>
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</tr>
<tr>
<td>EFV</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>FTC</td>
<td>↔</td>
<td>↔</td>
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</tr>
<tr>
<td>TFV</td>
<td>↔</td>
<td>↔</td>
<td>↑25%</td>
<td>↔</td>
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<tr>
<td>DRV</td>
<td>↔</td>
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<tr>
<td>RTV</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
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</tr>
<tr>
<td>RAL</td>
<td>↓ 27%</td>
<td>↓ 43%</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>RPV</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
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SOF can be co-administered with EFV, RPV, DRV/r, RAL or the NRTI FTC/TDF backbone

HIV/HCV co-infected subjects (n=223) treated with SOF + RBV for 12 or 24 weeks

Allowed HIV ARV regimens included FTC/TDF combined with any of following
- ATV/r, DRV/r, EFV, RAL, RPV

PK Results
- Similar SOF and GS-331007 exposure across HIV ARV regimens
- No clinically significant differences in SOF or GS-331007 PK compared with mono-infected HCV subjects

Kirby, et al. AASLD 2012.
P-gp–Mediated Probe Studies Across Programs

Effect on digoxin is mainly pre-systemic and modest
(AUC ↑ 34%)
LDV: Weak P-gp inhibitor

LDV as Perpetrator:
OCs
ARVs
Weak intestinal P-gp inhibition

Effect on digoxin is mainly pre-systemic and modest.
(AUC ↑ 34%)
GS-5816: Weak P-gp inhibitor

P-gp substrates allowed, caution warranted for narrow therapeutic (Digoxin)

OATP–Mediated DDIs

Background

- OATPs mediate hepatic uptake, thus DDIs in the setting of HCV therapy are of particular interest

- Many con meds/substrates are not specific OATP probes: multiple transporters and/or enzymes
  - Pravastatin: OATP1B1
  - Rosuvastatin: OATP1B1/3 and BCRP
  - No specific BCRP probe

- Goal: dissect contribution of multiple transporters by using multiple probes
OATP-Mediated DDIs Across Programs

**GS-9451/LDV/TGV**

- **Pravastatin (OATP):**
  - AUC ↑ 168%
  - C<sub>max</sub> ↑ 166%

**LDV**

- **Rosuvastatin (OATP/BCRP):**
  - AUC ↑ 699%
  - C<sub>max</sub> ↑ 1670%

**LDV as Perpetrator:**
- HCV DAA
- Weak OATP inhibition

**[LDV/SOF]**

- Pravastatin allowed,
- Rosuvastatin not recommended
OATP-Mediated DDIs Across Programs

GS-5816 (NS5A)

Pravastatin (OATP):
- AUC $\uparrow$ 35%
- $C_{\text{max}}$ $\uparrow$ 28%

Rosuvastatin (OATP/BCRP):
- AUC $\uparrow$ 169%
- $C_{\text{max}}$ $\uparrow$ 161%

GS-5816: Weak OATP Inhibitor
Moderate BCRP inhibitor

Weak inhibition of OATP by GS-5816 corroborates assertion of weak (or less) inhibition of OATP by LDV.

Pravastatin allowed,
Rosuvastatin dose limited to <10 mg/day

Transporters are here to stay and our understanding is increasing

- Multiple tools: conmed DDIs and probes will inform

DDI or probe study design (Single Agent vs Regimen) tailored to the projected regimen and known or potential liabilities

Data from regimen DDI or probe studies may be extracted to inform single agent or other multi-drug regimens

Multiple mixed probes can be used to dissect contribution of individual transporters