Clinical Pharmacology of DAA’s for HCV: What’s New and What’s in the Pipeline

Anita Mathias, PhD
Clinical Pharmacology, Gilead Sciences
14th Int. Workshop on Clinical Pharmacology of HIV Therapy
April 24th, 2013
Outline

• Background

• New DAA and Clinical Pharmacology Characterization
  • Sofosbuvir
  • Ledipasvir
  • GS-5816

• Going ahead
Background

• ~180 million people worldwide are infected with hepatitis C Virus (HCV) and ~3.2 million people in the US have chronic HCV infection

• Chronic HCV infection is a serious, progressive, and often life-threatening disease. If untreated, it can result in progressive liver fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma
  • Accounts for ~40% of all liver transplants in North America and Europe
  • Leads to ~10,000 deaths each year in the US

• Among patients infected with HCV worldwide, ~4 to 5 million are co-infected with HIV
  • In 2007, HCV surpassed HIV as a cause of death in the US
Current Treatment Options

- Primary objective of anti-HCV therapy is complete elimination of the virus, termed a sustained virological response (SVR)
- HCV is classified into at least 6 viral genotypes (GT)
- Genotype 1: Most common in North America and EU
  - PEG-IFN + RBV (24 – 48 Wks) + PI (Telaprevir OR Boceprevir) for 12 – 24 Wks
  - Duration guided by on-treatment response
- Genotype 2 & 3 (GT 3 more prevalent in EU)
  - PEG-IFN + RBV (24 Wks) (treatment naïve)
  - Re treat: PEG-IFN + RBV (48 Wks) (treatment experienced)
- Genotype 4, 5 and 6 (treatment naïve)
  - PEG-IFN + RBV (48 Wks)
- Key Special Populations
  - Liver Transplant (awaiting or received): No standard-of-care
  - HCV/HIV Coinfection: Few therapeutic options due to diminished efficacy and drug-drug interactions (DDIs)
Multiple Validated Drug Targets in HCV

<table>
<thead>
<tr>
<th>Host: IFN/ Cytokine</th>
</tr>
</thead>
</table>

### Table

<table>
<thead>
<tr>
<th>Phase</th>
<th>HCV PIs</th>
<th>NS5A Inhibitors</th>
<th>Cyclophilin Inhibitors</th>
<th>NS5B Nucs</th>
<th>NS5B Non-Nucs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td><strong>Boceprevir</strong>&lt;br&gt;<strong>Telaprevir</strong></td>
<td><strong>GS-5885 (Ledipasvir)</strong>&lt;br&gt;<strong>Daclatasvir</strong>&lt;br&gt;<strong>ABT-267</strong></td>
<td><strong>Alisporivir</strong>&lt;br&gt;<strong>Sofosbuvir</strong>&lt;br&gt;<strong>ABT-333</strong></td>
<td><strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>GS-5816</strong>&lt;br&gt;<strong>PPI-668</strong>&lt;br&gt;<strong>ACH-3102</strong>&lt;br&gt;<strong>IDX-719</strong>&lt;br&gt;<strong>MK-8325</strong>&lt;br&gt;<strong>MK-8742</strong>&lt;br&gt;<strong>GSK-625433</strong>&lt;br&gt;<strong>IDX-375</strong></td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td><strong>Simeprevir</strong>&lt;br&gt;<strong>Faldeprevir</strong>&lt;br&gt;<strong>Asunaprevir</strong></td>
<td><strong>GS-5885 (Ledipasvir)</strong>&lt;br&gt;<strong>Daclatasvir</strong>&lt;br&gt;<strong>ABT-267</strong></td>
<td><strong>Alisporivir</strong>&lt;br&gt;<strong>Sofosbuvir</strong>&lt;br&gt;<strong>ABT-333</strong></td>
<td><strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>GS-5816</strong>&lt;br&gt;<strong>PPI-668</strong>&lt;br&gt;<strong>ACH-3102</strong>&lt;br&gt;<strong>IDX-719</strong>&lt;br&gt;<strong>MK-8325</strong>&lt;br&gt;<strong>MK-8742</strong>&lt;br&gt;<strong>GSK-625433</strong>&lt;br&gt;<strong>IDX-375</strong></td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td><strong>GS-9451</strong>&lt;br&gt;<strong>Danoprevir</strong>&lt;br&gt;<strong>GS-9256</strong>&lt;br&gt;<strong>ABT-450</strong>&lt;br&gt;<strong>Vaniprevir</strong>&lt;br&gt;<strong>MK-5172</strong>&lt;br&gt;<strong>ACH-1625</strong>&lt;br&gt;<strong>GSK-2336805</strong></td>
<td><strong>GS-5885 (Ledipasvir)</strong>&lt;br&gt;<strong>Daclatasvir</strong>&lt;br&gt;<strong>ABT-267</strong>&lt;br&gt;<strong>GSK-2336805</strong>&lt;br&gt;<strong>SCY-635</strong>&lt;br&gt;<strong>Mericitabine</strong>&lt;br&gt;<strong>IDX-184</strong>&lt;br&gt;<strong>VX-135</strong>&lt;br&gt;<strong>Tegobuvir</strong>&lt;br&gt;<strong>VX-222</strong>&lt;br&gt;<strong>BI-207127</strong>&lt;br&gt;<strong>ABT-072</strong>&lt;br&gt;<strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>Alisporivir</strong>&lt;br&gt;<strong>Sofosbuvir</strong>&lt;br&gt;<strong>ABT-333</strong>&lt;br&gt;<strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>GS-5816</strong>&lt;br&gt;<strong>PPI-668</strong>&lt;br&gt;<strong>ACH-3102</strong>&lt;br&gt;<strong>IDX-719</strong>&lt;br&gt;<strong>MK-8325</strong>&lt;br&gt;<strong>MK-8742</strong>&lt;br&gt;<strong>GSK-625433</strong>&lt;br&gt;<strong>IDX-375</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 1</strong></td>
<td><strong>ACH-2684</strong>&lt;br&gt;<strong>MK-6325</strong>&lt;br&gt;<strong>MK-2748</strong>&lt;br&gt;<strong>GS-5816</strong>&lt;br&gt;<strong>PPI-668</strong>&lt;br&gt;<strong>ACH-3102</strong>&lt;br&gt;<strong>IDX-719</strong>&lt;br&gt;<strong>MK-8325</strong>&lt;br&gt;<strong>MK-8742</strong>&lt;br&gt;<strong>GSK-625433</strong>&lt;br&gt;<strong>IDX-375</strong></td>
<td><strong>GS-5885 (Ledipasvir)</strong>&lt;br&gt;<strong>Daclatasvir</strong>&lt;br&gt;<strong>ABT-267</strong>&lt;br&gt;<strong>GSK-2336805</strong>&lt;br&gt;<strong>SCY-635</strong>&lt;br&gt;<strong>Mericitabine</strong>&lt;br&gt;<strong>IDX-184</strong>&lt;br&gt;<strong>VX-135</strong>&lt;br&gt;<strong>Tegobuvir</strong>&lt;br&gt;<strong>VX-222</strong>&lt;br&gt;<strong>BI-207127</strong>&lt;br&gt;<strong>ABT-072</strong>&lt;br&gt;<strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>Alisporivir</strong>&lt;br&gt;<strong>Sofosbuvir</strong>&lt;br&gt;<strong>ABT-333</strong>&lt;br&gt;<strong>GS-9669</strong>&lt;br&gt;<strong>PF-868554</strong>&lt;br&gt;<strong>BMS-791325</strong>&lt;br&gt;<strong>ANA-598</strong></td>
<td><strong>GS-5816</strong>&lt;br&gt;<strong>PPI-668</strong>&lt;br&gt;<strong>ACH-3102</strong>&lt;br&gt;<strong>IDX-719</strong>&lt;br&gt;<strong>MK-8325</strong>&lt;br&gt;<strong>MK-8742</strong>&lt;br&gt;<strong>GSK-625433</strong>&lt;br&gt;<strong>IDX-375</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Under regulatory review
Sofosbuvir (SOF, formally GS-7977)

Potent HCV-specific nucleotide analog (chain terminator)

<table>
<thead>
<tr>
<th>Pangenotypic antiviral activity</th>
<th>High resistance barrier</th>
<th>Once daily 400 mg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short treatment duration</td>
<td>No response-guided therapy</td>
<td>Favorable safety profile and limited drug interactions</td>
</tr>
</tbody>
</table>

US NDA submitted April 8, 2013
Clinical Pharmacology- Intracellular Activation

- As nucleotide analog prodrug SOF is activated by sequential metabolic pathways including:
  - Low affinity and high capacity hydrolases (CES1, CatA and HINT1)
  - Nucleotide phosphorylation (UMP-CMP kinase and NDP kinase)
- Only SOF can enter hepatocytes and be converted to active TP (GS-461203)
- SOF can also undergo extrahepatic metabolism to form GS-331007 (predominant metabolite) principally eliminated in urine
• No evidence for FMO, UGT, or CYP450 mediated metabolism of SOF and GS-331007 (predominant circulating metabolite) in the clinic

• SOF but not GS-331007 is a substrate of Pgp and BCRP

• SOF and GS-331007 are not inhibitors or inducers of CYP450, UGT1A1 or drug transporters (Pgp, BCRP, OATP1B1, OATP1B3, OCT1, and BSEP)

  • GS-331007 showed no inhibition of the renal transporters OAT1, OAT3, OCT2, and MATE1

• GS-331007 accounts for >90% of systemic exposure to drug-related material

  • GS-331007 is considered to be the primary analyte of interest in clinical pharmacology studies for purposes of PK analyses and interpretation of results
Clinical Pharmacology - Clinical Studies

- 13 Phase 1 studies (healthy or HCV-infected subjects)
  - SAD, MAD, PK equivalence/food effect, mass balance, TQT, special populations (renal or hepatic impairment), drug-drug interaction studies with commonly administered concomitant medications

- **No dose adjustment of SOF is warranted in mild, moderate or severe hepatic impairment**

<table>
<thead>
<tr>
<th>Change in PK Parameter</th>
<th>Moderate Hepatic Impairment</th>
<th>Severe Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF</td>
<td>GS-331007</td>
</tr>
<tr>
<td>$AUC_{tau}$</td>
<td>↑126%</td>
<td>↑ 18</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>↑72%</td>
<td>↓6</td>
</tr>
</tbody>
</table>

- **No dose adjustment of SOF is warranted in mild or moderate renal impairment**

<table>
<thead>
<tr>
<th>Change in PK Parameter</th>
<th>Mild Renal Impairment</th>
<th>Moderate Renal Impairment</th>
<th>Severe Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF</td>
<td>GS-331007</td>
<td>SOF</td>
</tr>
<tr>
<td>$AUC_{inf}$</td>
<td>↑61</td>
<td>↑55</td>
<td>↑ 107</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>↑28</td>
<td>↑28</td>
<td>↑54</td>
</tr>
</tbody>
</table>
Clinical Pharmacology- Clinical Studies

• Drug Interaction Potential
  • Effect of SOF on the PK of Coadministered Drugs

<table>
<thead>
<tr>
<th>Change in PK Parameter</th>
<th>Cyclosporine A</th>
<th>Tacrolimus</th>
<th>R-Methadone</th>
<th>S-Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{\text{int or tau}}$</td>
<td>↔️</td>
<td>↔️</td>
<td>↔️</td>
<td>↔️</td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$</td>
<td>↔️</td>
<td>↓27%</td>
<td>↔️</td>
<td>↔️</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coadministered Drugs</th>
<th>Cyclosporine A</th>
<th>Tacrolimus</th>
<th>R-Methadone</th>
<th>S-Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>↔️</td>
<td>↔️</td>
<td>↔️</td>
<td>↓27%</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>↔️</td>
<td>↔️</td>
<td>↑25%</td>
<td>↓43%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>↔️</td>
<td>↔️</td>
<td>↑4%</td>
<td>↔️</td>
</tr>
<tr>
<td>Darunavir</td>
<td>↔️</td>
<td>↔️</td>
<td>↓15%</td>
<td>↔️</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↔️</td>
<td>↔️</td>
<td>↓27%</td>
<td>↔️</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>↔️</td>
<td>↔️</td>
<td>↑27%</td>
<td>↔️</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>↔️</td>
<td>↔️</td>
<td>↑154%</td>
<td>↔️</td>
</tr>
</tbody>
</table>

• Effect of Coadministered Drugs on the PK of SOF and GS-331007

<table>
<thead>
<tr>
<th>Change in PK Parameter</th>
<th>Cyclosporine A</th>
<th>Tacrolimus</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{\text{int or tau}}$</td>
<td>SOF</td>
<td>GS-331007</td>
<td>SOF</td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$</td>
<td>↑353%</td>
<td>↔️</td>
<td>↑13%</td>
</tr>
<tr>
<td>$\text{C}_{\text{tau}}$</td>
<td>↑154%</td>
<td>↓40%</td>
<td>↓4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coadministered Drugs</th>
<th>Cyclosporine A</th>
<th>Tacrolimus</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV/FTC/TDF; ATR</td>
<td>SOF</td>
<td>GS-331007</td>
<td>SOF</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>SOF</td>
<td>GS-331007</td>
<td>SOF</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↔️</td>
<td>↔️</td>
<td>↑34%</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>↔️</td>
<td>↔️</td>
<td>↓19%</td>
</tr>
</tbody>
</table>

Note: 90% CI of the GLSM ratio were within (↔️), extended above (↑), or extended below (↓) the predetermined equivalence boundaries of 70 to 143% or bioequivalence boundaries of 80%-125%.
Ledipasvir (LDV, GS-5885)

- HCV NS5A inhibitor
- Potent activity against GT1a and 1b

<table>
<thead>
<tr>
<th></th>
<th>GT 1a</th>
<th>GT 1b</th>
<th>GT 2a</th>
<th>GT 3a</th>
<th>GT 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC$_{50}$ (nM)</td>
<td>0.031</td>
<td>0.004</td>
<td>10.8</td>
<td>10.1</td>
<td>0.045</td>
</tr>
</tbody>
</table>

- Picomolar potency
- Potency maintained against cross-class resistant mutants (NS3: A156T, R155K, D168E, NS5B: S282T, Y448H)

- Safe and well tolerated in clinical studies to date
- Once daily
- Limited drug interactions
Clinical Pharmacology- Clinical Studies

Absorption
• Solubility-limited absorption

Metabolism and Elimination
• Low hepatic metabolic clearance and little renal excretion
• Not an inhibitor or inducer of P450 or UGT
• Likely substrate of Pgp
• Weak inhibitor of P-gp and BCRP (intestinal, but not systemic)
• Likely weak inhibitor of OATP1B1/OATP1B3

LDV may be co administered with
• P450 or UGT substrates
• P-gp inhibitors
• Moderate or hepatic Pgp and P450 inducers
• Acid reducing Agents
• No dose adjustment of LDV is warranted in mild or moderate hepatic impairment
• Renal impairment and severe hepatic impairment are ongoing
SOF and LDV Combination

• No clinically relevant drug-drug interaction between SOF and LDV
• No overlapping preclinical toxicology
• Both compounds have favorable DDI profile
• No food effect
SOF/LDV (FDC) Phase 3 Trial
ION-1 (TN, N=800) and ION-2 (TE, N=400)

Study Weeks

12w

24w

36w

SOF/LDV FDC

SOF/LDV FDC + RBV

SOF/LDV FDC*

SOF/LDV FDC + RBV

SVR12

SVR12

SVR12

*Arm 3 may be 12 or 24 weeks in ION-2 based upon emerging data
GS-5816

• Second generation potent, broad genotypic HCV NS5A inhibitor
• Potent activity (pM) against genotypes 1-6 replicons
• Safe and well tolerated in SAD/MAD First-In-Human study

Metabolism and Elimination

• High metabolic stability, and low systemic clearance in preclinical species

• Low potential for CYP450 mediated DDIs
  • Poor substrate for CYP2C8, CYP3A4, and CYP2B6
  • Not expected to be an inducer of AhR, or PXR

• Low potential for clinically relevant transporter based drug interactions
  • Weak inhibitor of P-gp or OATP 1B1/3
  • Modest inhibitor of BCRP; clinical relevance to be determined
Clinical Pharmacology-Clinical

- First-In Human Evaluation of GS-5816 reveals
  - Non linear (solubility-limited) PK across doses tested
  - Half-life (~15 hrs) supportive of once-daily dosing; modest accumulation on multiple dosing
  - $C_{\text{tau}}$ exceeded protein adjusted EC50 for all GTs at all evaluated doses
  - No appreciable food effect
  - In general, safety supports continued evaluation

- Proof of concept in GT 1 through 6 subjects ongoing
Gilead HCV Development Goals

Wave 1
GT 1: 3 drugs *(P/R/Protease Inhibitor)*

Wave 2
First all oral therapy GT2/3: *(SOF/R)*
Simplified, shorter therapy for GT1: *(SOF/P/R)*

Wave 3
GT1 First All Oral Therapies:
*(SOF/LDV FDC)*

Wave 4
All Oral Therapy for All HCV Genotypes
*(SOF/GS-5816; SOF/GS-"other")*