Drug-Drug Interactions of New HCV Drugs:

David Back
University of Liverpool
January 2015

11th Residential Course on Clinical Pharmacology of Antiretrovirals Torino
Approved Direct Acting Antivirals (DAA) and Drugs in Late Stages of Clinical Development

**NS3/4A Protease Inhibitors:**
- Boceprevir
- Telaprevir
- Simeprevir
- Paritaprevir
- Asunaprevir *in Japan*
- Vaniprevir *in Japan*
- Grazoprevir *(MK-5172)*
- Glecaprevir *(ABT-493)*
- GS-9451
- GS-9256
- Sovaprevir
- ACH-2684

**NS5A Inhibitors:**
- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbasvir *(MK-8742)*
- GS-5885
- Velpatasvir *(GS-5816)*
- Pibrentasvir *(ABT-530)*
- ACH-3102
- Samatasvir
- GSK2336805
- PPI-668

**Nucleos(t)ide Inhibitors:**
- Sofosbuvir
  - MK-3682
  - ACH-3422

- Non-Nucleoside Inhibitors:
  - Dasabuvir
  - Beclabuvir *(BMS-791325)*
  - GS-9669
  - PPI-383
  - TMC647055

* FDA decision 28th Jan 2016

Modified from Kiser J ICAAC Sept 2014
Overview

1. The Mechanisms of DDIs
2. Real World Data on DDIs
3. Emerging DDIs
4. Emerging DAAs
Overview

1 The Mechanisms of DDIs
Drug–drug interactions

Need to understand:
• The disposition or handling of each drug
• The therapeutic window of each drug
• Exposure – Response and Exposure – Adverse Response relationship to interpret pharmacokinetic (PK) data

Personal Communication: Professor D J Back
Gastrointestinal & Hepatic Metabolic/Transporter pathways for potential DDIs with DAAs

Also need to consider renal mechanisms

Adapted from Dick T et al Hepatology 2015 [Epub ahead of print]
# Mechanisms of Drug Interactions of DAAs

<table>
<thead>
<tr>
<th>DAA</th>
<th>Victim of DDI</th>
<th>Perpetrator of DDI</th>
<th>DDI Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>Substrate for CYP3A4, P-gp</td>
<td>Inhibits CYP3A4, P-gp &amp; OATP1B1/2</td>
<td>High</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Substrate for AKR, CYP3A4, P-gp, BCRP</td>
<td>Inhibits CYP3A4, P-gp</td>
<td>High</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r + dasabuvir (3D)</td>
<td>Substrate for CYP3A4, CYP2C8, OATP1B1/3, P-gp, BCRP</td>
<td>Inhibits CYP3A4, OATP1B1/3, OCT1, BCRP, P-gp, UGT1A1, CYP2C8, CYP2C19.</td>
<td>High</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Substrate for CYP3A4, P-gp &amp; OATP1B1</td>
<td>Inhibits gut CYP3A4, CYP1A2, OATP1B1 &amp; P-gp</td>
<td>Moderate</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Substrate for CYP3A4, P-gp</td>
<td>Inhibits OATP1B1, P-gp &amp; BCRP</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Substrate for P-gp &amp; BCRP, Gut pH</td>
<td>Inhibits P-gp &amp; BCRP</td>
<td>Moderate/Low</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Substrate for P-gp &amp; BCRP</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Available at [www.hep-druginteractions.org](http://www.hep-druginteractions.org) and relevant SmPCs ie Incivo (telaprevir), updated 27th July 2015; Victrelis (boceprevir), updated 5th March 2015; Viekirax (2D), updated 2nd Oct 2015; Exviera (dasabuvir) updated 2nd Oct 2015; Olysio (Simeprevir), updated 25th Aug 2015; Daklinza (daclatasvir), updated 30th Sept 2015; Sovaldi (sofosbuvir), updated 27th Aug 2015; Harvoni (LDV/SOF), updated 27th Nov 2015
Overview

2 Real World Data on DDIs
Drug–Drug Interactions With Novel All Oral Interferon-Free Antiviral Agents in a Large Real-World Cohort

Christoph Höner zu Siederdissen,1,8 Benjamin Maasoumy,1,8 Fiona Marra,2,3 Katja Deterding,1 Kerstin Port,1 Michael P. Manns,1 Markus Cornberg,1 David Back,2 and Heiner Wedemeyer1

1Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany; 2Department of Molecular and Clinical Pharmacology, University of Liverpool, and 3Pharmacy Department, Garthwaite General Hospital, Glasgow, Scotland, United Kingdom

Concomitant outpatient meds including OTC and herbals assessed in 261 HCV-monoinfected pts evaluated for antiviral treatment at Hannover Med School 2011-2014.

DDI between the outpatient med and DAAs evaluated using www.hep-druginteractions.org and prescribing information.
Drug-drug interactions with novel all oral interferon free antiviral agents – all issues solved?

Most patients treated for HCV infection take one or more drugs on a regular basis.
Drug-drug interactions with novel all oral interferon free antiviral agents – all issues solved?

<table>
<thead>
<tr>
<th>The 10 most common Drug Classes in regular outpatient medication list</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td>24.1</td>
</tr>
<tr>
<td>Beta Blockers (selective)</td>
<td>18.4</td>
</tr>
<tr>
<td>Aldosterone Antagonants</td>
<td>16.9</td>
</tr>
<tr>
<td>Thyroid Hormones</td>
<td>16.5</td>
</tr>
<tr>
<td>Angiotensin II Antagonants</td>
<td>13.0</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>11.1</td>
</tr>
<tr>
<td>Dihydropyridine derivatives</td>
<td>10.7</td>
</tr>
<tr>
<td>Thiazides</td>
<td>10.0</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>9.2</td>
</tr>
<tr>
<td>Beta Blockers (non selective)</td>
<td>8.0</td>
</tr>
</tbody>
</table>
Drug-drug interactions with novel all oral interferon free antiviral agents – all issues solved?

<table>
<thead>
<tr>
<th>DAA Regimen</th>
<th>% of Patients with AMBER DDIs</th>
<th>% of Patients with RED DDIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF/RBV</td>
<td>9.6</td>
<td>0</td>
</tr>
<tr>
<td>SOF/DAC</td>
<td>33.4</td>
<td>0.4</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>40.2</td>
<td>0</td>
</tr>
<tr>
<td>OBV/PTV/r + DSV (3D)</td>
<td>57.0</td>
<td>8.4</td>
</tr>
</tbody>
</table>

Individual ‘risk profile’ to cause potential DDIs with ‘regular’ medication
# Patient Comorbidities

**Table II - Most frequent comorbidities, by country**

<table>
<thead>
<tr>
<th></th>
<th>UK (n= 4,644)</th>
<th>Germany (n=2,735)</th>
<th>France (n=567)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidity</strong></td>
<td><strong>Prevalence</strong></td>
<td><strong>ICD10</strong></td>
<td><strong>Prevalence</strong></td>
</tr>
<tr>
<td>1 Depression</td>
<td>23.2%</td>
<td>Chronic pain syndromes (R52.1, R52.2, M54 (back pain))</td>
<td>22.7%</td>
</tr>
<tr>
<td>2 CVD</td>
<td>21.0%</td>
<td>Hypertension (I10)</td>
<td>22.1%</td>
</tr>
<tr>
<td>3 COPD/Asthma</td>
<td>14.4%</td>
<td>Depression (F32, F33)</td>
<td>14.7%</td>
</tr>
<tr>
<td>4 Pain</td>
<td>7.7%</td>
<td>Chronic Gastritis (K29)</td>
<td>10.7%</td>
</tr>
<tr>
<td>5 Substance use</td>
<td>4.1%</td>
<td>GORD (K20-23)</td>
<td>10.2%</td>
</tr>
<tr>
<td>6 GORD</td>
<td>3.4%</td>
<td>Polytoxicomania (F19)</td>
<td>9.2%</td>
</tr>
<tr>
<td>7 Diabetes</td>
<td>3.1%</td>
<td>Diabetes Type 2 (E11)</td>
<td>8.3%</td>
</tr>
<tr>
<td>8 Psychosis/Schizophrenia</td>
<td>3.0%</td>
<td>Dyslipidemia (E78)</td>
<td>6.6%</td>
</tr>
<tr>
<td>9 Epilepsy</td>
<td>2.3%</td>
<td>COPD (J44)</td>
<td>6.2%</td>
</tr>
<tr>
<td>10 Chronic Gastric</td>
<td>2.2%</td>
<td>Alcohol abuse (F10.2)</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

Legend: CVD – Cardiovascular Disease; COPD – Chronic Obstructive Pulmonary Disease; GORD – Gastro-oesophageal Reflux Disease
* As UK Read and ICD 10 code classification are incongruent, UK comorbidities cannot be directly compared with Germany and France comorbidities.
Always consider possible DDIs with co-medications

There is a need for robust data from DDI studies and clinical trials to support the use of concomitant medication with anti-HCV therapy
Overview

3 Emerging DDIs
### DDIs between HCV DAAs and cardiovascular drugs

<table>
<thead>
<tr>
<th>Antiarrhythmics</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>•</td>
<td>•</td>
<td>•</td>
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<tr>
<td>Digoxin</td>
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<tr>
<td>Flecanide</td>
<td>•</td>
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<tr>
<td>Vernakalant</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiplatelet and anti-coagulants</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
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<tbody>
<tr>
<td>Clopidogrel</td>
<td>•</td>
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<tr>
<td>Dabigatran</td>
<td>•</td>
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<tr>
<td>Warfarin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Beta blockers</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
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<tbody>
<tr>
<td>Atenolol</td>
<td>•</td>
<td>•</td>
<td>•</td>
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<tr>
<td>Bisoprolol</td>
<td>•</td>
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<tr>
<td>Propranolol</td>
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<table>
<thead>
<tr>
<th>Calcium channel blockers</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
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<tbody>
<tr>
<td>Amlodipine</td>
<td>•</td>
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<tr>
<td>Diltiazem</td>
<td>•</td>
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<tr>
<td>Nifedipine</td>
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<table>
<thead>
<tr>
<th>Hypertension and heart failure agents</th>
<th>SIM</th>
<th>DAC</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
</tr>
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<tbody>
<tr>
<td>Aliskiren</td>
<td>•</td>
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<tr>
<td>Candesartan</td>
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<tr>
<td>Doxazosin</td>
<td>•</td>
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<tr>
<td>Enalapril</td>
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</table>

FDA Drug Safety Communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni or Sovaldi) in combination with another Direct Acting Antiviral drug

[3-24-2015]

9 Cases: 3, LDV/SOF; 5, SOF/DAC; 1, SOF/SIM
6 cases within 24 h; 3 cases within 2-12 days of DAA

Amiodarone

- Class III antiarrhythmic
- Half life > 50 days
- Interacts with P-gp (transported by and inhibits)
- Several potential mechanisms have been put forward.

http://www.fda.gov/Drugs/DrugSafety
BRIEF REPORT

Extreme Bradycardia After First Doses of Sofosbuvir and Daclatasvir in Patients Receiving Amiodarone: 2 Cases Including a Rechallenge

Sophie Renet,¹,∗ Marie-Camille Chaumais,¹,²,3,∗ Teresa Antonini,³,4,5 Alexandre Zhao,⁶ Laure Thomas,⁷ Arnaud Savoure,⁸ Didier Samuel,³,4,5 Jean-Charles Duclos-Vallée,³,4,5 and Vincent Algalarondo³,6,9

Bradyarrhythmias Associated with Sofosbuvir Treatment

Fontaine H et al NEJM 2015; 373: 1886-1888

Interaction Between Amiodarone and Sofosbuvir-based Treatment for Hepatitis C Virus Infection: Potential Mechanisms and Lessons to be Learned

Back DJ & Burger DM Gastroenterology 2015; 149: 1345-1347
Mechanism of action of the Amiodarone – SOF/DAA interaction

1. SOF concentrations increased due to genetic factors* and transport inhibition by amiodarone

2. SOF/DAA affecting GI transport – with increase in amiodarone exposure? (amiodarone transport by P-gp)

3. Local effect of SOF/DAA on transporter(s) in cardiomyocyte – amiodarone accumulates in heart

4. Protein binding displacement – with increase in unbound amiodarone?
6 pts aged 60-75 on β-Blockers (nadolol, bisoprolol, metoprolol)
- Serial CV monitoring
- One pt had a HR decrease of 29 bpm (60 min post-dose).
  All other changes in HR and BP were modest.
- Asymptomatic
Treatment Outcomes With 8, 12 and 24 Week Regimens of Ledipasvir/Sofosbuvir for the Treatment of Hepatitis C Infection: Analysis of a Multicenter Prospective, Observational Study

N Terrault, S Zeuzem, AM Di Bisceglie, JK Lim, PJ Pockros, LM Frazier, A Kuo, AS Lok, ML Shiffman, Z Ben Ari, T Stewart, MS Sulkowski, MW Fried, and DR Nelson for the HCV-TARGET Study Group
HCV-TARGET: Status of LDV-SOF Treated G1 Patients

- **Consented**
  - N=2331
  - Not started (yet/or will not) for various reasons N=10

- **Started treatment**
  - N=2321
  - Still on treatment N=673

- **Ended treatment**
  - N=1648
  - Completed prior to 1 Jul’15 N=1270
  - Completed/After EOT cutoff date N=347
  - In post treatment F/U N=179

- **Lost in post treatment F/U**
  - N=17

- **LDV/SOF**
  - N=969
    - 8 wks N=154
    - 12 wks N=627
    - 24 wks N=161
    - Other+ N=27

- **LDV/SOF+RBV**
  - N=105
    - 12 wks N=89
    - 24 wks N=13
    - Other+ N=3

*SAEs reported for this population as SAE reporting is contemporaneous
**AEs reported for this population due to nature of data collection milestones
+ Other regimen durations did not satisfy a window of +/- 1 week to be included in the standard duration groups
HCV-TARGET: SVR12 with LDV/SOF Therapy by Subgroups

Includes patients receiving 8 (n=154), 12 (n=627), 24 (n=161) and other (n=27) week of therapy

Completed treatment as of 7/1/2015 and have available virological outcomes.

Patients who discontinued due to AE or were lost to follow-up are excluded.

SVR12: SVR at 12 (±1) weeks post treatment
HCV-TARGET: SVR12 by Use of PPI at Baseline with LDV/SOF

Should PPIs be contraindicated with SOF/LDV?

High percentage of HCV pts are on PPIs

Completed treatment as of 7/1/2015 and have available virological outcomes. Patients who discontinued due to AE or were lost to follow-up are excluded.
Effect of Food and Acid Reducing Agents on the Relative Bioavailability and Pharmacokinetics of Ledipasvir/Sofosbuvir Fixed-Dose Combination Tablet

Polina German, Jenny Yang, Steve West, Diana Chung, Anita Mathias
Gilead Sciences, Inc., Foster City, California

♦ LDV (single agent) exhibits pH-dependent solubility
  (Gilead Sciences, Inc., data on file)
  - LDV solubility is substantially higher under acidic versus neutral conditions (>1 mg/mL at pH 2 vs <0.1 µg/mL at pH 7)

♦ LDV/SOF may be administered with an H₂-receptor antagonist at a dose that does not exceed the equivalent of FAM 40 mg twice daily

♦ A PPI at a dose comparable to OME 20 mg may be administered simultaneously with LDV/SOF or up to 2 hours after taking LDV/SOF
Overview

4 Emerging DAAs
Grazoprevir and Elbasvir (Zepatier)

- **Grazoprevir (MK-5172)**
  - HCV NS3/4A inhibitor
  - 100 mg once-daily, oral

- **Elbasvir (MK-8742)**
  - HCV NS5A inhibitor
  - 50 mg once-daily, oral

- Broad *in vitro* activity against most HCV genotypes\(^1\)-\(^3\)
- Retains *in vitro* activity against many clinically relevant RAVs\(^1\)-\(^3\)
- All-oral, once-daily regimen

Grazoprevir

Drug-Drug Interaction Potential

**Victim:**
- Metabolised by CYP3A4
- Transported by P-gp & OATP1B1/3

**Perpetrator:**
- Inducer of -
- Inhibitor of BCRP
- Weak Inhibitor of CYP3A4
Elbasvir

Drug-Drug Interaction Potential

**Victim:** Metabolised by **CYP3A4**
Transported by **P-gp**

**Perpetrator:** Inducer of -
Inhibitor of **BCRP**
Minimal inhibitor of **P-gp**
GZR/EBR DDI RESULTS WITH COMMONLY USED HIV ART

<table>
<thead>
<tr>
<th>HIV ARV</th>
<th>Effect on GZR AUC</th>
<th>Effect on EBR AUC</th>
<th>Effect on Interacting Drug AUC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofovir disoproxil fumarate</td>
<td>← 0.9x</td>
<td>← 0.9x</td>
<td>↑1.2x with GZR</td>
<td>No adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑1.3x with EBR</td>
<td></td>
</tr>
<tr>
<td>raltegravir</td>
<td>← 0.9x</td>
<td>← 1.0x</td>
<td>↑1.4x with GZR</td>
<td>No adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑1.0x with EBR</td>
<td></td>
</tr>
<tr>
<td>dolutegravir</td>
<td>← 1.0x</td>
<td>← 1.0x</td>
<td>↑1.2x with GZR+EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>rilpivirine</td>
<td>← 0.9x</td>
<td>← 1.1x</td>
<td>← 1.1x with GZR+EBR</td>
<td>No adjustment</td>
</tr>
<tr>
<td>efavirenz</td>
<td>↓ 0.2x</td>
<td>↓ 0.5x</td>
<td>← 1.0x with GZR</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓0.8x with EBR</td>
<td></td>
</tr>
<tr>
<td>darunavir/ritonavir</td>
<td>↑ 7.5x</td>
<td>↑ 1.7x</td>
<td>←1.1x with GZR</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>←1.0x with EBR</td>
<td></td>
</tr>
<tr>
<td>atazanavir/ritonavir</td>
<td>↑ 10.6x</td>
<td>↑ 4.8x</td>
<td>↑1.4x with GZR</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>←1.1x with EBR</td>
<td></td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>↑ 12.9x</td>
<td>↑ 3.7x</td>
<td>←1.0x with GZR</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>←1.0x with EBR</td>
<td></td>
</tr>
</tbody>
</table>

Talaty et al., AASLD 2013; Caro et al., AASLD 2013; Yeh et al., CROI 2014; Yeh et al., CROI 2014; Yeh et al., CROI 2015; Yeh et al., IWCPHHT 2015
No Evidence of Pharmacokinetic Drug-Drug Interaction in Healthy Subjects Between Coadministered Grazoprevir (MK-5172)/Elbasvir (MK-8742) and Sofosbuvir

William L. Marshall¹; Wendy W. Yeh²; Crystal Bethel-Brown²; Daria Stypinski²; Patrice Auger²; Christine Brandquist²; Dana Gill²; John Brejda²; Luzeleena Caro³; Patricia Jumes³; Xiaobi Huang¹; Zifang Guo¹; Monika Martinho¹; H-P Feng¹; Danielle Armas²; Marian Iwamoto¹; Joan R. Butterton¹

¹Merck & Co., Inc., Kenilworth, NJ, USA; ²Celegion, Tempe, AZ, USA

No Pharmacokinetic Interaction Between HCV NS5A Inhibitor Elbasvir and Buprenorphine/Naloxone in Healthy Volunteers

William L. Marshall¹; Ted Maranco²; Hwa-Ping Feng³; April M. Barbour⁴; Jocelyn Gilmartin⁵; Fang Liu⁶; Deborah Panebianco⁷; Angela Mirtza⁸; Mike Di Spinho⁹; Daria Stypinski¹⁰; Ziv Machnes¹¹; Michael Gartner¹²; Marian Iwamoto¹³; Joan R. Butterton¹⁴; Wendy W. Yeh¹⁵

¹²Merck & Co., Inc., Kenilworth, NJ, USA; ³Celegion, Lincoln, NE, USA

No Pharmacokinetic Interaction Between HCV Inhibitors Grazoprevir/Elbasvir With Famotidine and Pantoprazole

Hwa-ping Feng¹; Patrice Auger²; Pavan Vaddadi³; Zifang Guo⁴; Fang Liu⁵; Deborah Panebianco⁶; Chun Feng⁷; Nadia Cardillo Mannico⁸; Vanessa Levine⁹; Luzeleena Caro¹⁰; David Hobbs¹¹; Michael Gartner¹²; Daria Stypinski¹³; Joan R. Butterton¹⁴; Marian Iwamoto¹⁵; Wendy W. Yeh¹⁶

¹⁷Merck & Co., Inc., Kenilworth, NJ, USA; ²Celegion, Lincoln, NE, USA

No Clinically Meaningful Pharmacokinetic Interactions Between HCV Inhibitors Grazoprevir/Elbasvir With Tacrolimus, Mycophenolate Mofetil, and Prednisone, But Cyclosporine Increases Grazoprevir/Elbasvir Exposures in Healthy Subjects

Wendy W. Yeh¹; Hwa-Ping Feng³; Katherine M. Dunne⁴; Nadia Cardillo Mannico⁸; Luzeleena Caro¹⁰; Zifang Guo⁵; Jennifer Talaty⁶; Dennis Wollord⁷; Michael Gartner¹²; Dennis Swearingen¹³; John Brejda¹⁴; Angela Cho²; William L. Marshall¹¹; Marian Iwamoto¹³; Joan R. Butterton¹⁴

¹¹Merck & Co., Inc., Kenilworth, NJ, USA; ²Celegion, Lincoln, NE, USA
Main Issue: Grazoprevir and Elbasvir as VICTIMS of DDIs via CYP3A4, OATP1B1, BCRP; but can be PERPETRATORS of few mainly transporter-mediated.
Velpatasvir

**Sofosbuvir/Velpatasvir**

- **Sofosbuvir (SOF)**
  - Potent antiviral activity against HCV GT 1–6
  - GS-331007: predominant circulating metabolite

- **Velpatasvir (VEL; GS-5816)**
  - Picomolar potency against GT 1–6
  - PK supports once-daily dosing

**Sofosbuvir/Velpatasvir**
- Treatment with SOF and VEL for 12 weeks resulted in high SVR in patients with GT 1–6
- Currently administered as once-daily FDC of SOF/VEL (400/100 mg)

FDC, fixed-dose combination; GT, genotype; PK, pharmacokinetics; SVR, sustained virologic response.
Velpatasvir

Drug-Drug Interaction Potential

**Victim:** Metabolised by: CYP3A4; CYP2C8; CYP2B6
Transported by: P-gp; BCRP; OATP

**Perpetrator:** Inducer of: -
Inhibitor of: P-gp; BCRP; OATP
Due to marked effect with EFV and also ~80% decrease in VEL exposure with Rifampicin* – VEL likely **contraindicated** with strong inducers.

SOF/VEL had no effect on exposure of EFV, RPV, DTG or RAL.

* Data from AASLD 2015; * Mogalian et al 15th IWCPHT, Washington 2014.
What about Tenofovir?

Coadministration of SOF/VEL with TDF-containing ART regimens increased TFV exposure by 40–81%.

- Relatively larger increase in TFV in the EFV/FTC/TDF group was likely related to fasted administration vs fed with other regimens
- Absolute TFV exposures were similar across cohorts
Effect of Velpatasvir on Rosuvastatin (BCRP/OATP substrate)

Test/Ref GMR (90% CI)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR (90% CI)</th>
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<tbody>
<tr>
<td>$\text{AUC}_{\text{inf}}$</td>
<td>2.69 (2.46, 2.94)</td>
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<tr>
<td>$\text{C}_{\text{max}}$</td>
<td>2.61 (2.32, 2.92)</td>
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Asunaprevir

Drug-Drug Interaction Potential

Victim: Metabolised by CYP3A4
Transported by OATP1B1

Perpetrator: Inducer of CYP3A4 (Weak)
Inhibitor of P-gp and OATP1B1 (Weak)
Inhibitor of CYP2D6 (Moderate)
Asunaprevir has a low potential to perpetrate drug–drug interactions via CYP3A4, P-glycoprotein and organic anion–transporting polypeptide (OATP), with no a priori dose adjustments required, but it is a moderate CYP2D6 inhibitor; coadministration of drugs that are substrates of CYP2D6 or P-glycoprotein and have a narrow therapeutic index should be undertaken with care.
Glecaprevir (ABT-493) & Pibrentasvir (ABT-530)

Key Pharmacokinetics:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- No renal excretion (<1%)

SURVEYOR-1: ABT-493 & ABT-530 for HCV GT1 Infection; AASLD 2015
Single Dose CsA gives ~30% increase in 493 and 20% in 530 (OATP1B1)

Multiple Dose ABT-493/530 gives ~50% increase in Tacrolimus (CYP3A4)
So ……

There are potential drug interactions with each of the DAA regimens

The KEY is management! If possible have good lines of communication between the physician and pharmacist.
Use a stepwise approach to DDI management

Is co-medication necessary?
- YES
  - Can the interaction be managed?
    - YES – no dose change required
      - Establish monitoring plan
        - Consult pharmacy to advise new dose
        - Establish monitoring plan
        - Change dose back on completion of treatment
    - YES – dose change required
      - Establish monitoring plan
      - Change to another clinically appropriate medicine
    - NO
      - Are there alternatives?
        - YES
          - Accept risk and proceed with care
          - Be aware of likely off-licence use of combination; look for toxicities and side effects associated with combined use
          - Establish robust clinical monitoring plan
      - NO

STOP
Thank You

Grateful to colleagues involved in www.hiv-druginteractions.org and www.hep-druginteractions.org and to colleagues involved in the EACS and EASL Guidelines

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