Pharmacology of HCV Therapy

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An Important Principle of Pharmacology: *Pharmacokinetics-Pharmacodynamics*

**Dose of drug administered** → **Drug in systemic circulation** → **Drug at site of action** → **Drug metabolised or excreted**

- **ABSORPTION**
  - Dose of drug administered
- **DISTRIBUTION**
  - Drug in systemic circulation
- **METABOLISM**
  - Drug metabolised or excreted
- **EXCRETION**
  - Drug at site of action

**PHARMACOKINETICS (PK)**
What the body is doing to the drug

**PHARMACODYNAMICS (PD)**
What the drug is doing to the body

**PHARMACOLOGICAL ie Virological EFFECT**
Important Pharmacokinetic Parameters following Oral Administration

- **Cmax**: Plasma concentration at maximum absorption.
- **Absorption phase**: The initial phase after oral administration.
- **Tmax**: Time to maximum concentration.
- **Elimination phase**: The phase where the drug is metabolized and excreted.
- **Half life (t1/2)**: Time taken for the drug concentration to reduce by half.
- **AUC**: Area under the curve, indicating total exposure to the drug.
- **Ctrough**: Plasma concentration at the lowest effective level.
- **Minimum effective conc**: Level needed to be effective.

**Graphical Representation**:
- **Absorption phase** shows the rapid increase in plasma concentration.
- **Elimination phase** shows a gradual decrease to the minimum effective concentration.
- **Dose 1** and **Dose 2** indicate the timing of drug administration.

**Legend**:
- **Blue area**: Represents the drug concentration over time.
- **Dots**: Indicate key points of interest such as Cmax and Ctrough.

**Additional Information**:
- **Plasma concentration** is plotted against time.
- **Dose 1** and **Dose 2** are marked at strategic points.
Important for successful outcome: Steady State & Therapeutic Window

Therapeutic Window

Therapeutic Failure / Toxicity

Therapeutic Success

Therapeutic Failure

( Dose Time)
Hepatitis C Virus

A positive strand RNA virus
The RNA genome translated into a polyprotein of ~ 3000 nucleotides
Interferon

- Extended plasma half life
- Reduced breakdown

Pegylation

Medscape
Interferon has a Dual Mechanism of Action: Viral Inhibition and Immune Modulation

- **Induction phase**: Inhibition of viral replication
- **Maintenance phase**: Immune system elimination of infected cells

Adapted from Ferenci P, et al. Viral Hep Rev 1999; 5: 229
### Ribavirin

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma half life</td>
<td>~ 300h on multiple dosing</td>
</tr>
<tr>
<td>Intracellular half life</td>
<td>~ ? h</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>55%. Recommended to be taken with food.</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>~ Does not bind</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly eliminated unchanged by <strong>renal</strong> excretion</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Difficult to use in pts with CrCl &lt; 50 ml/min</td>
</tr>
</tbody>
</table>
Ribavirin plasma concentrations over 24 wks

Interpatient variability (week 8): 31%; intrapatient variability (week 8-24): 10%
Mechanism of action of ribavirin

1. Modulation of TH1 & TH2 response.

2. Stimulation of interferon stimulated gene (ISG)

3. Inhibition of inosine monophosphate dehydrogenase (IMDH)
The addition of RBV Significantly Accelerates Viral Decay

- Peg alfa 2a 180μg/wk (n=17)
- Peg alfa 2a 180μg/wk plus ribavirin 1000–1200 mg/day (n=10)

Viral load (log_{10} IU/mL)

Days

Figure 1. Effect of HCV Therapy on Hemoglobin Levels

- **No treatment**: The blood hemoglobin level remains relatively stable throughout the treatment period, with slight fluctuations.
- **Interferon**: The hemoglobin level decreases significantly during the treatment period, reaching a lower level at the end of treatment.
- **Ribavirin**: The hemoglobin level decreases similarly to Interferon but slightly less compared to Interferon alone.
- **Interferon/Ribavirin combination**: The hemoglobin level decreases the most out of all the treatment groups, reflecting the combined effects of Interferon and Ribavirin.

End of Treatment is indicated at 24 weeks, showing a gradual return to baseline levels for all groups.
Progress in HCV Therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6 mo</th>
<th>IFN 12 mo</th>
<th>IFN/RBV 6 mo</th>
<th>IFN/RBV 12 mo</th>
<th>PEG IFN 12 mo</th>
<th>PEG IFN/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>6</td>
<td>16</td>
<td>34</td>
<td>42</td>
<td>39</td>
<td>54-56</td>
</tr>
</tbody>
</table>
Targets for New Hepatitis C Drugs

Ira Jacobson

Presented at the 6th Int. workshop on Hepatitis C – Resistance & New Compounds, 23 – 24 June 2011, Cambridge, USA
Treatment Targets against HCV

- Virion assembly
- Translation and polyprotein processing
- RNA replication
- Receptor binding and endocytosis
- Fusion and uncoating

Treatment:

Protease Inhibitors

- Boceprevir*
- Telaprevir*

*NS3/4A PIs

*Rockstroh J – personal communication
Examples of HCV NS5B polymerase inhibitors and their binding sites

Allosteric:
- Thumb 1
  - BI 207127
  - TMC 647055
- Allosteric GTP

Allosteric:
- Thumb 2
  - Thiophene
  - Filibuvir
  - GS 9669
  - VX 222

Allosteric:
- Palm
  - ABT 072
  - ABT 333
  - ANA 598

Active Site:
- Nucleosides
  - IDX 184
  - PSI 7977
  - RG 7128
Nucleotide analogs are chain-terminators

Nucleotide Chain-terminator (e.g., PSI-7977)

RNA chain cannot be elongated when analog is inserted

Mechanism of action, e.g., chain termination, does not rely on enzyme homology across HCV genotypes

Both pyrimidine and purine analogs can inhibit activity

Antiviral activity of nucleotides is conserved against PI-resistant or non-nuc polymerase inhibitor resistant virus
Mechanism of action and key attributes of cyclophilin inhibitor, alisporivir

Inhibition of Hepatitis C virus (HCV) replication

HCV replication complex (RC)

Cyclophilin (Cyp)

NS3, NS5A, or NS5B inhibitors

Direct Acting Antivirals (DAA)

ALISPORIVIR

Disruption of RC via inhibition of host proteins

Disruption of RC via inhibition of viral proteins

Key attributes of host-targeting antiviral (HTA), alisporivir

- Mechanism of action different from direct acting antivirals (DAA)
- High barrier for HCV resistance
- Compelling efficacy with pan-genotypic coverage
Administration of Boceprevir

- 4 x 200 mg capsules (800 mg) every 7-9 hours
- Boceprevir absorption is improved with food: +65%
  - Not dependent on fat intake
  - Recommended to administer boceprevir just before or after a meal
Administration of Telaprevir

- 2 x 375 mg pills (750 mg) every 7-9 hours
- Telaprevir absorption is improved with food
  - Standard fat \( \sim 20 \text{ g} = +237\% \); used in phase III trials
  - Recommended to ingest \( \sim 20 \text{ g} \) fat within 30 min
    - Bagel and cream cheese
    - 3 tablespoons peanut butter
    - 2 ounces cheddar cheese
## Disposition of the currently licensed DAAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing regimen</th>
<th>CYP metabolism</th>
<th>Non-CYP metabolism</th>
</tr>
</thead>
</table>
| **Telaprevir** | Q8h Taken with food (20 g of fat) | CYP 3A4:  
- Metabolised by  
- Markedly Inhibits | – |
| **Boceprevir** | 3 x daily Taken with food | CYP 3A4:  
- Metabolised by  
- Markedly Inhibits | AKR  
- Metabolised by |

➢ Also interactions emerging with transport proteins

AKR: aldo-keto reductase; DAA: direct-acting antiviral  
Q8h: every 8 hours; RTV: ritonavir; tid: three times daily
The importance of Cytochrome P450 (CYP) enzymes

CYP 3A isozymes are involved in the metabolism of majority of drugs

CYP 3A isozymes are present in human liver

CYP 3A isozymes are the most abundant in the liver

CYP 3A isozymes are involved in the metabolism of majority of drugs

CYP: cytochrome P450


All percentages are approximate. For illustrative purposes, hepatic CYP enzymes present at <5% are all represented as 3.3%
Enzyme inhibition and induction: effect of introducing another drug when steady state has already been reached

### Enzyme Inhibition

- **Drug Concentration (Drug Conc.)**
- **Days**

### Enzyme Induction

- **Drug Concentration (Drug Conc.)**
- **Days**

**Inhibiting Drug**

**Inducing Drug**
### Telaprevir & Boceprevir Increase Exposure to CYP3A Substrates: Perpetrator

<table>
<thead>
<tr>
<th>Drug</th>
<th>TVR Effect on the AUC (Exposure)</th>
<th>BOC Effect on the AUC (Exposure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A</td>
<td>4.6-fold increase</td>
<td>Manageable</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>70-fold increase</td>
<td>Difficult to manage</td>
</tr>
<tr>
<td>Midazolam</td>
<td>3.4-fold increase (i.v) 9-fold increase (oral)</td>
<td>6.3-fold increase (oral) Cl Dose reduce</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>7.9-fold CI</td>
<td>2.3-fold Cl</td>
</tr>
</tbody>
</table>

Telaprevir & Boceprevir decrease exposure to other CYP-metabolised drugs: 

**Perpetrator**

<table>
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<tr>
<th>Co-medication</th>
<th>TVR effect</th>
<th>BOC effect</th>
</tr>
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<tbody>
<tr>
<td>Escitalopram (SSRI) Metabolised by CYP2C19</td>
<td>↓ 35%</td>
<td>↓ 21%</td>
</tr>
</tbody>
</table>

- Mechanism: Not clearly determined
- Doses may need to be increased when combined with telaprevir; but dose adjustment not anticipated with boceprevir.

van Heeswijk R, et al. IWCPHT 2010. Abstract 12; Telaprevir EU SmPC; Hulskotte EGJ et al HEP Dart 2011; Abs 121; Boceprevir EU SmPC.
Enzyme inducing agents reduce telaprevir and boceprevir exposure: Victim

<table>
<thead>
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<th>Co-medications</th>
<th>Effect on telaprevir</th>
<th>Effect on boceprevir</th>
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</thead>
<tbody>
<tr>
<td>Efavirenz (600 mg qd)</td>
<td>↓ 26%</td>
<td>↓ 19% (Cmin 44%)</td>
</tr>
</tbody>
</table>

- Decrease in Telaprevir exposure substantially offset by increasing dose to 1125 mg q8h.

- The clinical outcome of the observed reduction of boceprevir concentrations has not been directly assessed.
Targeted drug-drug interaction studies are done in the development programme and some post-licensing.

Telaprevir and Boceprevir are *perpetrators* and *victims* of DDIs and this gives rise to a degree of nervousness.

Many DDIs can be explained on the basis of interaction with CYP3A4 *but not all.*

DAA: direct-acting antiviral; DDI: drug-drug interaction
HIV-HCV Co-Infection
The HCV-HIV interactions (Healthy volunteers) are: unexpected, inconsistent and difficult to explain.

Need information on pharmacokinetics in HCV patients – the magnitude of interactions maybe different.
– Interferon may be exerting enough anti HIV activity to protect against ‘low’ HIV drug concentration.

Perhaps total concentrations reduced but ‘free’ concentrations less affected – need data!

We do have ‘safer’ ARV options until there is clarity.
Management of Drug-Drug Interactions

LATEST ARTICLES
Guidelines - UK guidelines for boceprevir and telaprevir.
Meeting Report - 19th CROI, Seattle.
Review - Interactions with boceprevir and telaprevir.
Review - Entecavir
Drug Interactions - Telaprevir and midazolam or digoxin.
Drug Interactions - Warning with boceprevir and certain boosted HIV PIs.

Click here for previous news items

INTERACTION CHARTS FOR YOUR SMART PHONE

HEP iChart - a new app for mobile devices
Download for free to Android and Apple devices (search for HEP iChart)

Additional Comediations
In response to feedback about commonly prescribed comedications, ~40 new drugs have been added to th...

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DAAs as Components of New Treatment Paradigm for Hepatitis C

IFN-based

- 2009: Peg-IFN + RBV (SOC)
- 2011: 1 DAA + SOC
- ~2013: 2 DAAs + SOC
- 2015: IFN-free?

Prospect of shorter treatment duration for a greater proportion of patients

IFN-free?

DAA=direct-acting antiviral; SOC=standard of care (Peg-IFN + RBV)
Final Aim for a DAA Combination

- All oral
- QD (or BID)
- Safe & Tolerable
- Limited DDIs
- Pan-genotypes
- IL-28 Independent.
THANK YOU!