Drug-Drug Interactions in the Treatment of Hepatitis C

Jennifer J. Kiser, PharmD
University of Colorado Denver
Department of Pharmaceutical Sciences
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Objectives

• Compare and contrast the clinical pharmacology of BOC and TVR
• Identify therapeutic classes of drugs with the potential for drug interactions with BOC and TVR
• Discuss management of interactions with BOC and TVR
• Examine pharmacology and interaction potential of next “batch” of Hepatitis C agents
60% of marketed medications are metabolized by (or substrates for) CYP3A4*

Drugs that inhibit CYP3A raise concentrations of CYP3A substrates

Drugs that induce CYP3A lower concentrations of CYP3A substrates

CYP450 Inhibition

- **Drug Concentration**
- **Inhibiting drug added**
- **Time**
CYP450 Induction

Inducing drug added

Drug Concentration

Time
BOC and TVR are CYP3A substrates

- BOC and TVR PK affected by CYP3A inhibitor (ketoconazole) and inducer (efavirenz)
- Data presented as geometric mean ratios (GMR), i.e., ratio of concentrations A+B vs. A alone

<table>
<thead>
<tr>
<th></th>
<th>BOC GMR</th>
<th></th>
<th>TVR GMR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax</td>
<td>AUC</td>
<td>Cmin</td>
<td>Cmax</td>
</tr>
<tr>
<td>Ketoconazole(^a)</td>
<td>1.41(^1)</td>
<td>2.31(^1)</td>
<td>NR</td>
<td>1.24(^2)</td>
</tr>
<tr>
<td>Efavirenz(^b)</td>
<td>0.92(^1)</td>
<td>0.81(^1)</td>
<td>0.56(^1)</td>
<td>0.91(^3)</td>
</tr>
</tbody>
</table>

\(^a\) BOC: ketoconazole 400mg BID x 6 days, BOC single 400mg dose
TVR: ketoconazole single 400mg dose, TVR single 750mg dose

\(^b\) BOC: EFV 600mg QD x 16 days, BOC 800mg TID x 6 days
TVR: EFV 600mg QD x 20 days, TVR 750mg Q8H x 10 days

\(^1\) Kasserra C, et al. CROI 2011, Abstract 118, \(^2\)Garg V, et al. 6th IWCP Hepatitis Therapy, 2011, abstract PK-13,
\(^3\) van Heeswijk R, 18th CROI 2011, abstract 119
BOC and TVR are CYP3A Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Midazolam GMR</th>
<th>Atorvastatin GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Cmax</td>
</tr>
<tr>
<td>BOC</td>
<td>AUC$_{12}$ = 5.3$^1$</td>
<td>2.8$^1$</td>
</tr>
<tr>
<td>TVR</td>
<td>AUC$_{24}$ = 9.0$^2$</td>
<td>2.9$^2$</td>
</tr>
</tbody>
</table>

$^1$BOC: midazolam single 4mg oral dose, BOC 800mg TID x 6 days
$^2$TVR: midazolam single 2mg oral dose, TVR 750mg Q8H x 11 days,
$^3$40mg single dose
$^4$20mg daily

- TVR a more potent CYP3A inhibitor

Interactions Can Occur at Level of Drug Transport
Major Renal Transporters

- Basolateral (BL): OCT2, OCT3, OAT1, OAT2, OAT3
- Brush Border (AP): ISBT, PEPT1, PEPT1, URAT1, OATP1, OAT4
- Urinary Lumen: P-gp, MRP2, MRP4, MATE1

Role in renal secretion and reabsorption

Efflux: P-gp, MRP2, MRP4, MATE1
Uptake: OCT2, OCT3, OAT1, OAT2, OAT3

Blood flow from Basolateral (BL) to Urinary Lumen.
Concept of a Therapeutic Index

Intensity of overall exposure to an antiviral drug

Probability of Effect (%)

Viral Inhibition

Toxicities

Pharmacokinetic Variability – Food, Genetics, Degree of Liver Damage, Body Weight

Intensity of overall exposure to an antiviral drug
Approach to Identifying and Managing Drug Interactions in HCV Treatment

Kiser JJ, Burton JR, Everson GT. Nature Reviews Gastro & Hepatol [Accepted]
Patient Case

• 45 year old Caucasian male being considered for triple therapy for HCV
  – Genotype 1a
  – 2/2012 biopsy
    • moderate activity (grade 3 of 4)
    • portal and periportal fibrosis (stage 2 of 4)
  – 7/2012 HCV RNA = 3,010,000 IU/mL (log_{10} 6.48)

• Comorbidities and Medications:
  – Hyperlipidemia: atorvastatin 10mg QHS
  – Hypertension: metoprolol 50mg BID, lisinopril 10mg QD
  – Depression: sertraline 150mg QD
  – Erectile Dysfunction: sildenafil 50mg prn
  – Chronic pain: oxycodone 5mg Q6H prn
How do we manage hyperlipidemia while on BOC or TVR?

1. No change, the low dose (10mg) of atorvastatin is safe with BOC and TVR
2. Change the atorvastatin to simvastatin
3. Change the atorvastatin to pravastatin
4. We don’t. Stop the atorvastatin for now and re-start once the HCV PI course is completed.
## HMG Co-A Reductase Inhibitors

<table>
<thead>
<tr>
<th>Statin</th>
<th>Route of Metabolism</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>CYP3A4++</td>
<td>Avoid use with BOC and TVR</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>CYP3A4++</td>
<td>Avoid use with BOC and TVR</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP3A4+</td>
<td>Avoid use with TVR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Start with lowest ATOR dose with BOC and do not exceed 40mg QD</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Minimal metabolism, slight 2C9 and 2C19</td>
<td>No data</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Multiple routes, primarily glucuronidation</td>
<td>No data with TVR, BOC ↑ PRAV 60%</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Multiple routes including CYP2C9,3A4,2D6,2C8</td>
<td>No data</td>
</tr>
</tbody>
</table>
Antihypertensives

• ACE inhibitors and diuretics ok
• Metabolized to some extent by CYP3A, so consider dose reductions
  – Beta blockers: carvedilol and nabivolol
  – ARBs: irbesartan and losartan
• Calcium channel blockers
  – Amlodipine Cmax and AUC increased 1.27- and 2.79-fold by TPV, so a reduced dose should be considered
Antidepressant Exposures Likely Reduced by BOC and TVR

Escitalopram AUC ↓ 21% by BOC (t₁/₂ ↓ from 31 to 22 hrs)¹

With HIV protease inhibitors, paroxetine and sertraline exposures are reduced.³,⁴

¹Hulskotte EGJ, et al. HepDART 2011,
³van Heeswijk R, et al. 5th IWCP Hepatitis Therapy, Boston, MA 2010, abstract 12
³Best BM, et al. 14th CROI 2007, abstract 574
⁴Sekar V, et al. 8th International Congress on Drug Therapy in HIV Infection 2006, abstract P295
How do we treat erectile dysfunction?

1. Current dose of sildenafil is fine for occasional use
2. Reduce sildenafil dose to not exceed 25mg in 48 hours
3. Switch to tadalafil, dose should not exceed 10mg in 72 hours
4. Discontinue use of erectile dysfunction agent during treatment
# Interactions with Ritonavir and Erectile Dysfunction Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Fold Change in AUC with RTV</th>
<th>Modified Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>50 mg qd</td>
<td>$11^1$</td>
<td>25 mg q 48h</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>10 mg qd</td>
<td>$49^2$</td>
<td>2.5 mg q 72h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>($T_{1/2} = 26h$)</td>
<td></td>
</tr>
<tr>
<td>Tadalafil</td>
<td>10 mg qd</td>
<td>$2.2^3$</td>
<td>10 mg q 72h</td>
</tr>
</tbody>
</table>

1 studied with RTV 500 mg BID  
2 studied with RTV 600 mg BID  
3 studied with RTV 200 mg BID
Opioids

• Primarily metabolized by CYP3A, so may require dose reduction:
  – Oxycodone
  – Tramadol
  – Fentanyl

• Hydrocodone, codeine, morphine, hydromorphone, oxymorphone okay
Interaction Potential of Concomitant Medications with BOC and TVR

<table>
<thead>
<tr>
<th>Avoid or Use With Caution (Requires Investigation)</th>
<th>Safe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Contraceptives</td>
<td>Psychotropics</td>
</tr>
<tr>
<td>Phosphodiesterase Inhibitors</td>
<td>Herbal Supplements</td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitors</td>
<td>Pain Medications</td>
</tr>
<tr>
<td>Antiretroviral Drugs</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>Antimycobacterials</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Antifungals</td>
</tr>
<tr>
<td>Ergot Derivatives</td>
<td>Alpha-1 adrenoreceptor antagonist</td>
</tr>
</tbody>
</table>
How long does it take for the inhibition effects of TVR and BOC to wear off?

1. Immediately following the last dose
2. One half-life of the drug (i.e., 9-11 hour for TVR and 1-3 hours for BOC)
3. One week
4. One month
Resources for Drug Interactions

• University of Liverpool
  – www.hep-druginteractions.org

• Toronto General Hospital
  – http://www.hcvdruginfo.ca/

• University of Buffalo ACTG Pharmacology Support Laboratory
  – http://tdm.pharm.buffalo.edu/home/di_search/
# Pharmacology and Interaction Potential of Phase 3 Agents

<table>
<thead>
<tr>
<th></th>
<th>CYP3A substrate?</th>
<th>Interaction Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faldaprevir (PI)</td>
<td>√</td>
<td>Moderate ∩ CYP3A, weak ∩ CYP2C9,¹ ∩ UGT1A1²</td>
</tr>
<tr>
<td>Simeprevir (PI)</td>
<td>√</td>
<td>Mild ∩ CYP1A2 and intestinal 3A4,³ ∩ OATP1B1 and MRP2⁴</td>
</tr>
<tr>
<td>Daclatasvir (NS5A)</td>
<td>√</td>
<td>Substrate and ∩ of P-gp</td>
</tr>
<tr>
<td>Sofosbuvir (NI)</td>
<td>X</td>
<td>Transporters? Intracellular phosphorylation?</td>
</tr>
</tbody>
</table>

¹Sabo JP, 52nd ICAAC 2012, ²Sane R, 46th EASL 2011, ³Sekar V, 45th EASL 2010, ⁴Huisman MT, 61st AASLD 2010,
Conclusion

- BOC and TVR have complex pharmacology
- Interactions are not easily predicted
- Identification and management of interactions is critical with these agents
- Next “batch” of Hepatitis C agents less likely to act as perpetrators in interactions but still victims