Itraconazole and Clarithromycin as Ketoconazole Alternatives for Clinical CYP3A Inhibition Studies to Quantify Victim DDI Potential

Alice Ban Ke, Ph.D.
Consultant & Scientific Advisor
Simgyp Limited
Alice.Ke@certara.com

2014 AAPS Annual Meeting and Exposition
PPDM Mini-Symposium
Nov 5th, 2014

Disclosure: The work presented was conducted at Eli Lilly and Company. The views expressed represent the personal views of the authors.
Outline

• CYP3A inhibitor(s) selection
• Pharmacokinetic and DDI properties
• Predictability of DDI magnitude using PBPK models
• Pros and cons of using the proposed CYP3A inhibitors
• Opportunities for PBPK modeling
  - Optimal DDI study designs
  - Extrapolate to ketoconazole DDI outcomes
• 45% (10/22) of NMEs approved in 2013 are substrates of cytochrome P450 3A (CYP3A)

• High-dose ketoconazole (400 mg q.d. for ≥5 days) has been the gold-standard strong CYP3A inhibitor in drug development drug–drug interaction (DDI) studies

✓ The increase in systemic exposure to the substrate due to ketoconazole treatment provides an estimate of fraction metabolized by CYP3A

✓ Represent the worst-case DDI scenario

• In 2013, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) advised against using this ketoconazole regimen following review of clinical safety reports

• These regulatory actions present a significant obstacle in the context of drug development process

• Acceptable alternatives to ketoconazole are needed
Systematic evaluation of 21 strong (midazolam AUCR ≥ 5) CYP3A inhibitors described in 2012 FDA and EMA DDI guidances and UW Drug Interaction Database

- The majority of these drugs are not suitable as ketoconazole alternatives in healthy-volunteer DDI studies.
- Low-dose ritonavir (100 mg b.i.d. for ≥10 days) is the most common, strong CYP3A inhibitor used in the development of anti-viral agents.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>CYP3A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not available in the US</td>
<td>unapproved: troleandomycin, mibefradil, nefazodone, stand-alone cobicistat; unapproved for oral use: conivaptan; restricted use due to safety: telithromycin.</td>
</tr>
<tr>
<td>Borderline moderate to high CYP3A inhibitors (approximately 5-fold Midazolam AUCR)</td>
<td>posaconazole, boceprevir, saquinavir, nelfinavir</td>
</tr>
<tr>
<td>Drugs used exclusively in combination with ritonavir</td>
<td>lopinavir, indinavir, tipranavir, elvitegravir</td>
</tr>
<tr>
<td>Non-specific CYP3A inhibition</td>
<td>voriconazole, ritonavir (also due to clinical safety issues, including hepatotoxicity, pancreatitis, and lipid disorders)</td>
</tr>
<tr>
<td>Safety issues</td>
<td>telaprevir (black box warning for potentially lethal skin reactions)</td>
</tr>
</tbody>
</table>
Clarithromycin (CLA) and itraconazole (ITZ) were identified as the inhibitors that best met all four criteria

1. **Potency (ranked by clinical AUC ratio of sensitive CYP3A-substrate drugs)**

   - ITZ and CLA are two strong clinical CYP3A inhibitors

   - Both ITZ (maximal midazolam AUCR = 10.8; 200 mg q.d. for 4 days) and CLA (maximal midazolam AUCR = 8.4; 500 mg b.i.d. for 7 days) are clinically less potent than the standard high-dose ketoconazole regimen (AUCR = 16.7; 400 mg q.d. for 4 days)

   - More comparable to low-dose ketoconazole (AUCR = 9.2; 200 mg q.d. for 3 days)

   - Therefore, ITZ and CLA may not directly represent the worst-case DDI scenario
2. Specificity (not a potent inhibitor of other major CYP enzymes, P-gp and OATP1B1/1B3)

- Both ITZ and CLA are specific CYP3A inhibitors
  - Ketoconazole is weak CYP2C8 and CYP2C9 inhibitor

- Both are P-gp inhibitors
  - ITZ (200 mg q.d. for 5 days) and CLA (500 mg b.i.d. for 7 days) increased oral digoxin AUC 1.7-fold and 1.6-fold, respectively
  - Ketoconazole (400 mg q.d. for 8 days) similarly elicited a 2.5-fold increased exposure to dabigatran, an intestinal P-glycoprotein probe drug

- CLA (but not ITZ) may be a moderate clinical inhibitor of OATP1B1
  - CLA (500 mg b.i.d. for 9 days) increased oral pravastatin (40 mg q.d. for 15 days) AUC 2.1-fold
3. **Clinical safety**

- The CLA and ITZ label contain information in the ‘warnings’ (not boxed warning) regarding risks of rare, sometimes severe hepatotoxicity, and the risk of QT prolongation (CLA only). However, these potential risks to DDI study subjects are low and manageable.

- Mild and transient elevations in liver enzymes occur in 4% to 20% of patients on oral ketoconazole, in 1% to 5% of patients on ITZ, in 1-2% of patients treated for short periods and a higher proportion of patients given CLA long-term (http://livertox.nlm.nih.gov/)

- Antibiotic resistance may be a concern with CLA

- The available published literature does not allow a clear judgment of whether ITZ has improved safety with respect to liver injury risk compared to ketoconazole (Greenblatt et al., Journal of Clin Pharm, 2014. DOI: 10.1002/jcph.400)
Clarithromycin (CLA) and itraconazole (ITZ) were identified as the inhibitors that best met all four criteria

1. **Potency** (ranked by clinical AUC ratio of sensitive CYP3A-substrate drugs)
   - ITZ and CLA are two strong clinical CYP3A inhibitors
   - Similar inhibitory effects as the low-dose ketoconazole

2. **Specificity** (not a potent inhibitor of other major CYP enzymes, P-gp and OATP1B1/1B3)
   - Both ITZ and CLA are specific CYP3A inhibitors
   - Both are P-gp inhibitors
   - CLA (but not ITZ) may be a moderate clinical inhibitor of OATP1B1

3. **Clinical safety**
   - The CLA and ITZ label contain information in the ‘warnings’ (not boxed warning) regarding risks of rare, sometimes severe hepatotoxicity, and the risk of QT prolongation (CLA only). However, these potential risks to DDI study subjects are low and manageable
   - Antibiotic resistance may be a concern with CLA

4. **Quantitative predictability of the DDI magnitude**
Clarithromycin (CLA) PK and DDI properties

- Extensive metabolism by CYP3A
- Exhibits dose-dependent pharmacokinetics
- Elimination half-life increases from 3-4 hours at 250mg BID to 5-7 hours at 500mg BID
- Irreversible and competitive inhibitor specific to CYP3A
- Also a P-gp inhibitor (↑ digoxin p.o. AUC by 1.6-fold) and OATP1B1 inhibitor (↑ pravastatin p.o. AUC by 2.1-fold)
Predictive performance of Simcyp v12.2 CLA model: pred./obs. midazolam AUCR ranged from 0.75 to 1.26

Summary: pros and cons of using CLA (500 mg b.i.d. for 7 days) as CYP3A inhibitor

- CLA produces irreversible, persistent inhibition of CYP3A
- Requires long pre-treatment period of 7 days to achieve maximal CYP3A inhibition
- Compared to 1-2 days for ketoconazole, which has inhibitory effects that are of rapid onset and rapid reversibility
- Requires long recovery period of 7–10 days to allow complete restoration of intestinal and hepatic CYP3A activity levels
- CLA inhibits intestinal CYP3A activity more efficiently than hepatic CYP3A activity
- CLA inhibits hepatic transporter OATP1B1, therefore can produce greater DDI magnitude for a victim drug that is substrate of both CYP3A and OATP1B1 versus inhibition of CYP3A alone (e.g. ITZ or ketoconazole)

3.7 X Bosentan AUC (125 mg b.i.d. for 14 days)

Figure 2
Effect of 4 days of clarithromycin co-administration (△) on bosentan pharmacokinetics (steady state; ○). Pooled data of 16 healthy volunteers with different CYP2C9 and SLCO1B1 genotypes

Market et al., Br J Clin Pharmacol 2014
• Significant food effect on the absorption of ITZ (food increased ITZ AUC by 1.6-2.6 fold)
• Its bioavailability (~0.55) and half-life (~21 hr) are dose-dependent
• Extensive and saturable metabolism by CYP3A
• Accumulation ratio is 2.5-fold following once daily dosing for 7 days
• Reversible inhibitor specific to CYP3A; Also a P-gp inhibitor (↑ digoxin AUC by 1.7-fold)
• The metabolites of ITZ have been predicted to account for ~50% of the overall CYP3A4 inhibition in vivo
Sequentially formed ITZ metabolites predicted to contribute to *in vivo* CYP3A4 inhibition observed after ITZ dosing

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>R</th>
<th>Unbound $K_i$</th>
<th>Predicted % contribution to CYP3A inhibition ($I_{u,ss}/K_{i,u}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>$R = \text{CH-CH}_2\text{-CH}_3$</td>
<td>1.3 nM</td>
<td>50-60%</td>
</tr>
<tr>
<td>Hydroxyitraconazole</td>
<td>$R = \text{CH-CH}_2\text{-CH}_3$</td>
<td>14.4 nM</td>
<td>20-40%</td>
</tr>
<tr>
<td>Ketoitraconazole</td>
<td>$R = \text{CH-CH}_2\text{-CH}_3$</td>
<td>7.0 nM</td>
<td>10%</td>
</tr>
<tr>
<td>N-Desalkylitraconazole</td>
<td>$R = \text{H}$</td>
<td>0.44 nM</td>
<td>10%</td>
</tr>
</tbody>
</table>

Templeton et al., Clin Pharmacol Ther 2008
Predictive performance of modified Simcyp ITZ model (accounting for OHITZ): pred./obs. midazolam AUCR ranged from 0.57 to 1.37

<table>
<thead>
<tr>
<th>ITZ</th>
<th>50 mg SD solution</th>
<th>200 mg SD solution</th>
<th>400 mg SD solution</th>
<th>200 mg SD for 6 days</th>
<th>100 mg QD for 4 days</th>
<th>200 mg QD for 6 days</th>
<th>200 mg QD for 4 days</th>
<th>200 mg QD for 4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>2 mg po taken 4 hours after the inhibitor dose</td>
<td>2 mg po taken 4 hours after the inhibitor dose</td>
<td>2 mg po taken 4 hours after the inhibitor dose</td>
<td>7.5 mg po taken 2 hours after the inhibitor dose on day 1</td>
<td>0.05 mg/kg IV over 2 min 2 hours after the inhibitor dose on day 4</td>
<td>7.5 mg po taken 2 hours after the inhibitor dose on day 4</td>
<td>7.5 mg po taken 2 hours after the inhibitor dose on day 6</td>
<td>15 mg po taken 2 hours after the inhibitor dose on day 4</td>
</tr>
<tr>
<td>Demographics of HVs (M:F)</td>
<td>n=6 (5:1); Age 22-42 yrs;</td>
<td>n=6 (5:1); Age 22-42 yrs;</td>
<td>n=6 (5:1); Age 22-42 yrs;</td>
<td>n=12 (7:5); Age 19-25 yrs; Weight 57-95 kg</td>
<td>n=12 (7:5); Age 19-25 yrs; Weight 57-95 kg</td>
<td>n=12 (4:8); Age 19-40 yrs; Weight 54-98 kg</td>
<td>n=12 (7:5); Age 19-25 yrs; Weight 57-95 kg</td>
<td>n=9 (5:4); Age 22-34 yrs; Weight 55-78 kg</td>
</tr>
</tbody>
</table>
Challenges: inconsistent plasma protein binding data in literature: 0.2%-3.6% for ITZ; 0.5-2% for OHITZ

- Relative contribution of ITZ and OHITZ to CYP3A inhibition \textit{in vivo}?
Challenges: sequentially formed ITZ metabolites predicted to contribute to in vivo CYP3A4 inhibition observed after ITZ dosing

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Unbound $K_i$</th>
<th>Predicted % contribution to CYP3A inhibition ($I_{u,ss}/K_{i,u}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>$\text{CH}_3 \quad \text{R} = \text{CH}-\text{CH}_2-\text{CH}_3$</td>
<td>1.3 nM</td>
<td>50-60%</td>
</tr>
<tr>
<td>Hydroxyitraconazole</td>
<td>$\text{CH}_3 \quad \text{R} = \text{CH}-\text{CH}-\text{CH}_3$</td>
<td>14.4 nM</td>
<td>20-40%</td>
</tr>
<tr>
<td>Ketoitraconazole</td>
<td>$\text{CH}_3 \quad \text{R} = \text{CH}-\text{C}-\text{CH}_3$</td>
<td>7.0 nM</td>
<td>10%</td>
</tr>
<tr>
<td>N-Desalkylitraconazole</td>
<td>R = H</td>
<td>0.44 nM</td>
<td>10%</td>
</tr>
</tbody>
</table>

Templeton et al., Clin Pharmacol Ther 2008
Knowledge gaps: *in vitro* and *in vivo* evaluation of CYP3A inhibitor transport by hepatic OATP

**Blood oral exposure**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ketocazole</th>
<th>Itraconazole</th>
<th>OH-Itraconazole</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng*h/mL)</td>
<td>100000</td>
<td>10000</td>
<td>1000</td>
<td>100</td>
</tr>
</tbody>
</table>

**Hepatic distribution**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ketocazole</th>
<th>Itraconazole</th>
<th>OH-Itraconazole</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Kp</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

- As for ITZ and OHITZ
  - Oral AUC was not increased in the absence of hepatic Oatps
  - Liver Kp was not decreased in the absence of hepatic Oatps
- Consistent with negative *in vitro* OATP1B1/3 transport data (HEK293 cells expressing OATP1B1,1B3 and 2B1, human hepatocyte ± BSP)
- Rules out active hepatic uptake via OATPs

Higgins et al., Drug Metab Dispos. 2014
Persistent inhibition of CYP3A by ITZ

• The inhibition of CYP3A by ITZ *in vivo* is persistent, which exceeds in duration four half-lives of ITZ
  - tacrolimus, cyclosporine, triazolam
  (Trenk et al., 1987; Cervelli and Russ, 2003; Neuvonen et al., 1996)

• Believed to be due to long elimination half-life of ITZ and its inhibitory metabolites

• The developed PBPK model successfully predicted the persistent effect of ITZ on midazolam

![Graph showing Midazolam AUC ratio during ITZ treatment and after its discontinuation](image)

Observed data: Backman et al., Eur J Clin Pharmacol 1998
Summary: pros and cons of using ITZ (200 mg q.d. for 4-6 days) as CYP3A inhibitor

- Relatively long pre-treatment period to achieve maximal CYP3A inhibition (*versus* 1-2 days for ketoconazole)

- Need to consider the impact of formulation and food intake on ITZ absorption

- ITZ produces persistent inhibition of CYP3A due to long elimination half-life of ITZ and its inhibitory metabolites

- ITZ inhibits hepatic CYP3A activity more efficiently than intestinal CYP3A activity

- Need to assay multiple analytes (ITZ, OHITZ, NDITZ) in plasma samples collected from DDI studies

- Modest under-prediction of midazolam AUCRs using ITZ PBPK model is evident

- ITZ dose used in literature DDI studies was not high enough and/or the duration of treatment was not long enough
Opportunities for PBPK modeling: itraconazole DDI study design considerations

Itraconazole dosing regimens

• ITZ dose used in literature DDI studies was not high enough and/or the duration of treatment was not long enough

• 15 days to attain steady-state exposure

• 200 mg BID on day 1, then 200 mg QD on days 2-6 attained similar ITZ and OHITZ exposures and DDI effect (Midazolam AUCR=9.0) as dosing 200 mg QD for 15 days
Opportunities for PBPK modeling: itraconazole DDI study design considerations

Impact of formulation and food intake on DDI outcome

- Model predicted a modest increase in midazolam AUCR following ITZ tablet administration in the fed state compared to the fasted state.

- Recommend the use of ITZ solution (low food and pH absorption effects) to circumvent the potential impact of food intake on victim drug DDI.

- ITZ oral solution exhibits an earlier Tmax (1-2.5 hours) than the tablet (3-4 hrs).

Simultaneous versus staggered dosing time of ITZ and victim drug

For long half-life victim drugs, number of doses of ITZ needed post victim administration to attain the maximal AUCR.
Opportunities for PBPK modeling: extrapolating ITZ or CLA DDI outcomes to ketoconazole DDI outcomes (or vice versa)

Estimate \( f_m \) and \( F_g \) of the victim drug

- The key is to obtain an independent estimate of either fraction metabolized by CYP3A \( (f_{m,3A}) \) or intestinal availability due to CYP3A \( (F_{g,3A}) \).

- An estimate of \( F_{g,3A} \) can be obtained from in vitro data, estimated indirectly from observed overall bioavailability and hepatic availability, or estimated by fitting a PBPK model to both i.v. and oral pharmacokinetic profiles.

- Alternative is to utilize DDI outcomes obtained from two CYP3A modulators.

Observed AUC ratio is 6.2

Han et al. Manuscript in preparation, 2014
Conclusions

• Itraconazole (200mg b.i.d. on day 1, q.d. on days 2-6) and clarithromycin (500mg b.i.d. for 7 days) are two strong clinical CYP3A inhibitors that possess the desirable features of selectivity, safety, and quantitative predictability.

• Itraconazole and clarithromycin may not directly assess the worst-case DDI scenario, but this shortcoming can be bridged through modeling.

• Challenges exist in further-refinement of the inhibitor PBPK models.

• Once model fidelity is validated, there are tremendous opportunities of applying model-based approach to address study design issues, data interpretation and extrapolate to unstudied scenarios.