Perspective from IQ working group on 4β-HC in Drug Development

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On behalf of the IQ 4β-HC Working Group
March 17, 2017
ASCPT
Response of 4β-HC to CYP3A Inducers in Patients

- At least 3 weeks of treatment may be needed to differentiate strong/moderate/weak CYP3A inducers by the 4β-HC increase
Response of 4β-HC to CYP3A Inducers, Inhibitors and Mixed inhibitor/inducer in Healthy Volunteers and Patients

- **RIF in HV**
  - 4b-HC
  - 6b-OHC/C
  - MDZ CL (IV)
  - MDZ CL (PO)
  - Midostaurin CL (PO)
  - Quinidine CL (PO)

- **Dose escalation of RIF**
  - Normalized 4b-HC
  - 6b-OHC/C
  - MDZ CL (PO)
  - Quinidine CL (PO)

- **CYP3A Inhibitors**
  - 4b-HC
  - 6b-OHC/C
  - MDZ CL (IV)
  - MDZ CL (PO)

- **Mixed CYP3A inhibitor and inducer**
  - 4b-HC
  - MDZ CL (IV)
  - MDZ CL (PO)
Recommendations for the Application of 4β-HC in Drug Development

Advantages of 4β-HC
Minimally invasive
Cost-effective biomarker of hepatic CYP3A

- Applications for CYP3A induction:
  - Multiple dose study
  - Replace dedicated midazolam DDI study?
  - CYP3A activity at baseline and during efficacy studies
Recommendations: Multiple dose study

Advantages

- In a study with at least 6 subjects and one week of treatment, an increase in 4β-HC provides an early signal for strong hepatic CYP3A inducers.

- If the NME is not a CYP3A inducer *in vitro*, monitoring 4β-HC may confirm the absence of hepatic CYP3A induction in an appropriately designed study.

Limitations

- The magnitude of the 4β-HC change is smaller than the magnitude of an oral midazolam clearance change.

- If no change in 4β-HC is observed, one cannot rule out the risk of weak and moderate hepatic CYP3A induction, intestinal CYP3A induction or CYP3A inhibition.
Recommendations: Replace Dedicated Midazolam DDI study?

Limitations

- 4β-HC is unlikely to replace an oral midazolam DDI study because 4β-HC is insensitive to acute CYP3A inhibition or short-term treatment and will not reflect intestinal CYP3A DDIs

Advantages

- 4β-HC may be used for long-term treatment studies or in patient populations where a midazolam DDI study is not feasible/practical
- Normalized 4β-HC is recommended when the treatment affects cholesterol levels
Recommendations:
CYP3A Activity at Baseline and During Efficacy Studies

Advantages
– Reflects inter-individual variability in hepatic CYP3A
– Maybe suitable for chronic condition in which hepatic CYP3A activity is altered by disease

Limitations
– Does not reflect intestinal CYP3A activity
– May be insensitive to mild disease states or diseases involving acute or local inflammation
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Reference

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Kasichayanula BJCP 2014
Niemi Pharma 2006
Goodenough CRT 2011
Dutreix EJCP 2014
Kanebratt CPT 2008
Marde Arrhen CPT 2008

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Josephson EJCP 2008
Mao DMR 2016
A Case Example of Application of 4β-HC in a Discovery Project: How to Translate the Preclinical in vitro and in vivo Data to Assess Human CYP3A Induction Risk?

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March 17, 2017
ASCPT
Compound X: exposure of Day 7 significant lower than Day 1 in cynomolgus monkey toxicology study

<table>
<thead>
<tr>
<th>Dose 100mg/kg</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 7/Day1 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-12&lt;/sub&gt; free (µM*h)</td>
<td>45.4</td>
<td>9.9</td>
<td>-78.2</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; free (µM)</td>
<td>7.0</td>
<td>2.1</td>
<td>-70.0</td>
</tr>
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Questions:
- What is the main cause in the decreased exposure in monkey?
- Will it occur in human?
Overall Strategy for CYP3A induction risk assessment

**Cyno induction risk**

- **Observed D7 vs. D1 exposure**

  - Monitor hepatic CYP3A biomarker 4ß-HC in the toxicology studies

  - CYP3A biomarker helps to understand whether the decreased exposure of D7 compared to D1 is related to CYP3A8 induction in cynomolgus monkey

  - If yes, it is important to find means to increase the dose in order to cover the high dose for toxicology studies

**Human induction risk**

- **Build model using human in vitro data**

  - Measured induction potency in validated human hepatocytes

  - PBPK (Simcyp)

  - Predict human PK

  - Predict MDZ-DDI

- **Observed exposure in multiple dose study**

  - Monitor hepatic CYP3A biomarker 4ß-HC in multiple dose study in Phase I
Auto-induction was confirmed by the increase in 4β-HC

Two fold increase of plasma 4β-HC concentration confirmed the auto-induction hypothesis.

Put into context: Four fold increase was observed for 16 days of RIF treatment @15 mpk/day (DMD 42: 839-43)

<table>
<thead>
<tr>
<th></th>
<th>D1 150 mg/kg</th>
<th>D7 150 mg/kg</th>
<th>D7/D1 %</th>
<th>D1 250 mg/kg</th>
<th>D7 250 mg/kg</th>
<th>D7/D1 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-12}$ free (µM*h)</td>
<td>38.5</td>
<td>8.9</td>
<td>-76.9</td>
<td>52.3</td>
<td>9.3</td>
<td>-82.2</td>
</tr>
<tr>
<td>C$_{\text{max}}$ free (µM)</td>
<td>5.0</td>
<td>1.9</td>
<td>-62</td>
<td>5.8</td>
<td>2.4</td>
<td>-58.7</td>
</tr>
</tbody>
</table>
Human PK and DDI prediction of compound X

PK
- Compound X was predicted with a moderate clearance and low Vss, considered a reasonable IVIVE in preclinical species
- No impact of auto-induction on its PK was predicted with the worst case scenario.

DDI
- Low CYP3A induction risk was predicted at the efficacious dose.

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D7</th>
<th>D7/D1%</th>
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<tbody>
<tr>
<td>Scenario fmcyp3A=0.9 with mRNA induction data*</td>
<td></td>
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<tr>
<td>AUC(_{0-12}) free (µM.h)</td>
<td>4.9</td>
<td>4.8</td>
<td>-3</td>
</tr>
<tr>
<td>C(_{\text{max}}) free (µM.h)</td>
<td>2.7</td>
<td>2.7</td>
<td>-1</td>
</tr>
<tr>
<td>C(_{\text{min}}) free (µM.h)</td>
<td>0.0088</td>
<td>0.0079</td>
<td>-10</td>
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<table>
<thead>
<tr>
<th>CYP3A probe</th>
<th>Midazolam</th>
<th>Geometric mean % (95% CI)</th>
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<tbody>
<tr>
<td>AUC ratio</td>
<td>-16 (-18, -15)</td>
<td></td>
</tr>
<tr>
<td>C(_{\text{max}}) ratio</td>
<td>-12 (-13, -11)</td>
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* Compound X mRNA CYP3A EC50=41.2-77.6 µM, Emax= 17.8-25.9
Conclusion

• 4β-HC is minimally invasive and cost-effective biomarker of hepatic CYP3A in both monkey and human.

• Monitoring the change of 4β-HC can serve as a practical solution to understand whether the CYP3A8 induction is contributing to the exposure decrease in monkey.

• A positive readout of 4β-HC in monkey provides the valuable insight in a timely manner without performing the isolation of liver tissue or monkey hepatocyte induction study or monkey DDI study.

• By applying PBPK approach in preclinical species with the measured in vitro data and observed PK profiles, one can form a strategy with a relatively higher confidence on key parameter prediction for human PK and DDI risk assessment.
Acknowledgements

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Human PK prediction strategy using PBPK approach

- Observed IV and PO PK profile in preclinical Species
- Measured in vitro data for preclinical
- Form a PBPK strategy on key parameters prediction for human based on four preclinical species
- Predict human PK
- IVIVE Confidence
- Measured in vitro data for human