Endogenous Biomarkers for the Evaluation of CYP3A-mediated Drug Interactions

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# Evaluation of Drug-Drug Interactions

## In Vitro DDI Assessment

- **How to assess the DDI potential?**
- **What should be my clinical DDI assessment strategy?**
- **Which clinical DDI studies should I conduct?**

*Focuses on enzyme- and transporter-based DDI*

## Clinical DDI Studies

- **When to conduct needed clinical DDI studies?**
- **How should clinical DDI studies be conducted?**
- **How should results from clinical DDI studies be analyzed, interpreted, managed and communicated?**

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*Modified from Dinko Rekić, ASCPT 2016*
Goals of Drug Interaction Evaluation

• Determine the potential for clinically significant DDIs

• Determine management strategies for clinically significant DDIs
Types of DDI Studies

• In vitro
  – Inhibition
  – Induction
  – Mixed

• Clinical
  – Prospective or Retrospective
  – Index studies (studies with index perpetrators and index substrates)
  – Concomitant use studies

• In silico
Index studies

• Use perpetrators or substrates with **well defined properties** (level of inhibition, induction, and metabolic pathway)

• **Extrapolate** to other substrates and perpetrators

• May not be clinically relevant for intended patient population
Index substrates predictably exhibit exposure increase due to inhibition or induction of a given metabolic pathway and are commonly used in prospective clinical DDI studies.

For example, midazolam is a sensitive index substrate for CYP3A.
Endogenous Biomarker (vs. Probe Substrate) for DDI Evaluation

Advantages:
• Obviates the need to administer a probe drug
• Patient population

Challenges:
• May not be used to evaluate gut enzymes
• Variability (baseline, diurnal variation)
Biomarkers of CYP3A activity

Questions

• What have we learned?
• Are we ready to utilize biomarkers to replace clinical DDI studies?
# 4β-Hydroxycholesterol (4β-HC) for CYP3A DDI Evaluation

- 5 NDA submissions (2013-2016)

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NME as CYP3A modulator</strong>&lt;br&gt;(1 case) &lt;br&gt;In vitro-inhibitor and inducer for CYP3A &lt;br&gt;In vivo-no effect on CYP3A</td>
<td>Both 4β-HC and CYP3A substrate results showed that CYP3A levels did not change significantly in the presence of NME. DDI results with the CYP3A substrate were included in the labeling.&lt;br&gt;(Results of biomarker were not included in the labeling.)</td>
</tr>
<tr>
<td><strong>NME as CYP3A substrate</strong>&lt;br&gt;(4 cases)</td>
<td>Supportive to show that CYP3A was induced in the presence of known inducer.</td>
</tr>
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</table>

NME: new molecular entity
# Urinary 6β-Hydroxycortisol (6β-OHC) for CYP3A DDI Evaluation

- 7 NDA submissions (2013-2016)

## Purpose

<table>
<thead>
<tr>
<th>NME as CYP3A inducer (5 cases)</th>
<th>Purpose</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>in vitro/in vivo→labeling</td>
<td>6β-OHC was used to study the effect of multiple dose NME on CYP3A activity</td>
<td>Conclusions in the labeling were generated from overall assessments. The sources of information (e.g., biomarker) were not mentioned in the labeling.</td>
</tr>
<tr>
<td>1 +/- → n/a</td>
<td>2 cases had separate studies with *CYP3A substrates</td>
<td></td>
</tr>
<tr>
<td>1 +/- (*/+) → +</td>
<td>3 cases no other studies with CYP3A substrates</td>
<td></td>
</tr>
<tr>
<td>1 +/- (in vivo dose was not high enough) → n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 -/± (variable) (*-) → negative in vitro data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 +/- -/→ -</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>NME as CYP3A substrate (3 cases)</th>
<th>Purpose</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6β-OHC was used to show CYP3A change in the presence of the known inducer (e.g., rifampin)</td>
<td>Supportive to show that CYP3A was induced in the presence of known inducers.</td>
<td></td>
</tr>
</tbody>
</table>

NME: new molecular entity; n/a: not available (drug was not approved).
## Comparison of 4β-HC and Midazolam for DDI Evaluation

<table>
<thead>
<tr>
<th></th>
<th>4β-HC</th>
<th>Midazolam (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selectivity for CYP3A</strong></td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td><strong>DDI type and sensitivity</strong></td>
<td>-Induction -Not sensitive to inhibition (long-half life)</td>
<td>Sensitive to both inhibition and induction</td>
</tr>
<tr>
<td><strong>DDI magnitude and quantification</strong></td>
<td>Smaller dynamic range</td>
<td>Change in CL larger</td>
</tr>
<tr>
<td><strong>DDI site</strong></td>
<td>Hepatic</td>
<td>Intestine and hepatic</td>
</tr>
</tbody>
</table>
Comparison of 4β-HC and Midazolam with Varying Induction Potencies

**Table 1. Inducer Classification and Corresponding Model-Predicted 4βHC Biomarker Changes**

<table>
<thead>
<tr>
<th>Regulatory CYP3A Inducer Classification</th>
<th>Midazolam AUC GMR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Population PK/PD&lt;sup&gt;c&lt;/sup&gt;</th>
<th>( E_{\text{max}}^{-1}_{\text{max}} )</th>
<th>Bayesian Mechanism—Based PK/PD&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>0.50–0.80</td>
<td>(&lt;1.13)</td>
<td>1.09–1.37</td>
<td>1.05–1.20</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.20–0.50</td>
<td>1.13–2.10</td>
<td>1.37–2.46</td>
<td>1.20–2.05</td>
</tr>
<tr>
<td>Strong</td>
<td>0.20</td>
<td>( &gt;2.10)</td>
<td>( &gt;2.46)</td>
<td>( &gt;2.05)</td>
</tr>
</tbody>
</table>


<sup>b</sup>AUC, area under plasma concentration-time curve; GMR, geometric mean ratio.

<sup>c</sup>From Ref. 8.

<sup>d</sup>From Ref. 7.

**Table 2. Model-Predicted 4βHC Increase From Baseline Median (5th and 95th Percentiles) After 14 Days of Treatment With Rifampicin**

<table>
<thead>
<tr>
<th>Rifampicin Dose (mg)</th>
<th>Predicted Median (5th, 95th Percentiles)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>1.13 (1.04, 1.44)</td>
</tr>
<tr>
<td>20</td>
<td>1.28 (1.10, 1.71)</td>
</tr>
<tr>
<td>100</td>
<td>2.10 (1.45, 3.49)</td>
</tr>
<tr>
<td>500</td>
<td>4.43 (2.63, 6.77)</td>
</tr>
<tr>
<td>600</td>
<td>4.76 (3.00, 6.77)</td>
</tr>
</tbody>
</table>

<sup>a</sup>4βHC, 4β-hydroxycholesterol.
When May 4β-HC be Used for DDI Assessment

• Determine the potential for clinically significant DDIs
  - May detect NMEs that are “stronger” CYP3A inducer
  - May miss NMEs that are “weaker” CYP3A inducers
  - May not provide an accurate DDI assessment for NMEs that are mixed CYP3A inhibitors/inducers
  - Cannot be used to study for CYP3A inhibition

• Determine management strategies for clinically significant DDIs
  
  How to extrapolate the results “quantitatively” to other CYP3A substrates to inform dosing adjustment?
Conclusions

• New research has been conducted in the biomarker area
• We have limited regulatory experience on the use of endogenous biomarkers (e.g., 4β-HC) for DDI evaluation.
• There are areas that endogenous biomarkers can be used to assess DDI
  – For example, 4β-HC for qualitative assessment of hepatic CYP3A induction
  – Limitation and scope of each marker need to be well understood with proper validation to fit the intended purpose of the evaluation.
• Currently, 4β-HC study alone is unlikely to replace an oral midazolam study as an “index” substrate
  – Can 4β-HC data coupled with PBPK modeling be able to quantitatively predict the effect on CYP3A induction?
Acknowledgements

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Sam Rebello (co-chair) and other speakers in this workshop
What is an Ideal Universal DDI Biomarker?

- **Selectivity** - Good specificity
- **DDI Type and Sensitivity** - Sensitive to changes in enzyme activity (either inhibition or induction)
- **DDI magnitude and quantification** - Quantitative correlation with the known index substrate change in a similar magnitude in response to enzyme activity change
- **DDI site** - Can detect both intestinal and hepatic enzyme changes