Risk Assessment for Drug-Drug Interactions in Early Development

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Biomarkers of CYP3A Activity:
What Have We Learned and are We Ready to Utilize Biomarkers to Replace Clinical DDI Studies?

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CASE STUDY 1
A clinical study is often required to put perspective on in vitro results that indicate a drug is a perpetrator of CYP3A DDI (or other enzyme/transporter -inhibitor or inducer)

- Midazolam is a common probe substrate for the clinical DDI study to assess CYP3A perpetrator potential

- A biomarker assay to assess CYP3A modulation could provide some assessment prior to a formal DDI

- Potential resource savings by delaying study

- Potential to replace formal DDI once validated?

- Urinary 6β-OH-cortisol, 6β-OH-cortisone, and plasma 4β-OH-cholesterol are considered to be predictive markers of CYP3A activity; however, the signal for inhibition using these markers is much less robust than the signal for induction

- A recently published paper by Shin et al. suggests that the CYP3A-mediated inhibition with midazolam clearance could be predicted using a combination of urinary DHEA levels, 7β-hydroxy-DHEA:DHEA ratios, 6β-hydroxyxycortisone: cortisone ratios, and CYP3A5 genotype
Combined Evaluation of MAD & DDI with Midazolam

Assess the effect of Compound A on PK of midazolam and 1-OH midazolam.
Assess the effect of Compound A on 7β-OH-DHEA:DHEA & 6β-OH-cortisone: cortisone urine excretion ratios

MAD Evaluation
- Compound A 2.5 mg QD 14 days

DDI Evaluation
- Day -1 Midazolam only
- Day 1-12 40 mg Compound A (or Placebo)
- Day 13 Midazolam+ 40 mg Compound A (or Placebo)

Compound A
- 100 mg QD 14 Days
- 40 mg QD 14 Days
- 10 mg QD 14 Days
- 2.5 mg QD 14 Days

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Ratios of 7 Beta-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone were not dose dependent and there was substantial inter-subject variability.
The Change in AUCs of Midazolam and 1-OH-midazolam Before and After Dosing with 40 mg of Compound A

Preliminary data from both midazolam and 1-hydroxymidazolam suggest that Compound A has minimal effect on CYP3A activity and the disposition of 1-OH-midazolam
The Correlation of Mean Ratios of 1’-OH-Midazolam/Midazolam, 7β-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone are Directionally Similar

Mean Ratios of 1’-OH-Midazolam/Midazolam, 7β-OH-DHEA/DHEA and 6β-OH-Cortisone/Cortisone were consistent in terms of demonstrating lack of an effect of Compound A on CYP3A4 Activity.
CASE STUDY 2
Introduction & Rationale

• In Vitro Data Suggested Compound B has a Dual Potential for Induction and Inhibition for CYP3A4
  • At therapeutic concentrations inhibition was observed with an IC50 of 6.4 µM using midazolam as a probe
  • Induction was also noted with a 4-fold increase in mRNA over control at 2.5 µM
• The overall long-term effect on CYP3A4 was difficult to predict
• In order to inform the Phase 2 program in a timely manner, we proposed DDI Strategy as a tiered approach
  • Perform a standard cocktail DDI study to address inhibitory potential at the highest potential therapeutic dose of 350 mg QD
  • In parallel, monitor 4β-OH-cholesterol in the MAD to determine whether induction would occur
• Results from the 4β-OH-cholesterol evaluation in the MAD would inform the need for further induction studies
DDI Study Suggested Compound B inhibited CYP3A4 Resulting in Increased Midazolam & Decreased 1-OH Midazolam Exposure

<table>
<thead>
<tr>
<th>Analyte</th>
<th>GMR (90% CI) AUC</th>
<th>GMR (90% CI) Cmax</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1.23 (1.09, 1.39)</td>
<td>1.13 (1.01, 1.26)</td>
<td>Weak Inhibition</td>
</tr>
<tr>
<td>1-OH Midazolam</td>
<td>0.88 (0.74, 1.03)</td>
<td>0.76 (0.60, 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

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4β-OH-cholesterol data from MAD Study Suggested Potential for Induction

- Meaningful increases (~70%) were observed only at the highest dose panel of 350 mg
- Compared to strong inducers like rifampin, data suggests that compound B may not be a strong inducer for CYP3A4
- However, the potential for weak or moderate induction remained a question
Study Design for Repeat Cocktail DDI Study: *Multiple Dose Levels and Longer Duration of Treatment*

**BMS cocktail probes**
- Midazolam (3A4): 5 mg
- Digoxin (p-gp): 0.25 mg
- Montelukast (2C8): 10 mg
- Flurbiprofen (2C9): 50 mg
- Omeprazole (2C19): 40 mg

**BMS drug treatment cohorts**
- Cohort 1: Compound B, 200 mg, QD
- Cohort 2: Compound B, 350 mg, QD

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Compound B Caused Time-dependent Alterations in the PK of Midazolam

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Duration</th>
<th>GMR (90 CI) Cmax</th>
<th>GMR (90 CI) AUC(INF)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>4 days</td>
<td>1.06 (0.87, 1.30)</td>
<td>1.10 (0.93, 1.31)</td>
<td>Weak inhibition</td>
</tr>
<tr>
<td>200</td>
<td>14 days</td>
<td>0.85 (0.68, 1.06)</td>
<td>0.73 (0.59, 0.91)</td>
<td>Weak induction</td>
</tr>
<tr>
<td>350</td>
<td>4 days</td>
<td>1.21 (1.08, 1.35)</td>
<td>1.21 (1.13, 1.30)</td>
<td>Weak inhibition</td>
</tr>
<tr>
<td>350</td>
<td>14 days</td>
<td>0.92 (0.81, 1.05)</td>
<td>0.69 (0.60, 0.80)</td>
<td>Weak induction</td>
</tr>
</tbody>
</table>

Conclusion: The long-term effect of administration of Compound B was weak induction of CYP3A4. Therefore, no dosage adjustments for sensitive substrates of CYP3A4 are warranted.
Conclusions from Case Studies

• In general, biomarkers are a useful tool to detect potential DDI signals
• From these 2 case studies, biomarkers were predictive of the direction of the DDI
• With agents that have the potential for dual inhibition and induction it remains difficult to predict the net effect of long-term administration
• Clinical studies with probe studies are still needed to confirm the extent of the DDI
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