DDI Assessment for Therapeutic Proteins and ADCs

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Disclaimer

Aspects of this presentation reflect the views of the speaker and may not necessarily reflect official FDA, DHHS or other government opinion or policy.

The case examples are illustrative in nature to facilitate discussion and are not meant to be construed as current requirements.
BLA Approvals

• 30% of CDER novel drug approvals in 2016 and 2017 (so far) were BLAs

DDIs in TPs: Important or not?

• Some therapeutic protein (TP) labels have no Section 7 (Drug Interactions)

7 DRUG INTERACTIONS

Since ZINPLAVA is eliminated by catabolism, no metabolic drug-drug interactions are expected [see Clinical Pharmacology (12.3)].
TP- Drug Interactions

• *Pharmacokinetic (PK) Effect
  – **Perpetrator**- pro-inflammatory cytokines/CYP450s
  – **Victim** - generally limited interactions for TPs
    • Effect on immunogenicity (i.e., infliximab & MTX)
    • Other mechanisms? (i.e., palifermin & heparin)
  – **Antibody-drug conjugates (ADCs)** – DDIs for payloads

• Pharmacodynamic and toxicity-related interactions

* I will focus on PK interactions today
7.1 Immunosuppressive or Immune-Modulating Therapies

The concomitant use of OCREVUS and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with OCREVUS. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS [see Warnings and Precautions (5.2)].

Ocrelizumab- CD20 directed Ab (Approved 2017)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf

7.1 Alendronate

Co-administration of alendronate and NATPARA leads to reduction in the calcium-sparing effect, which can interfere with the normalization of serum calcium. Concomitant use of NATPARA with alendronate is not recommended.

7.2 Digoxin

NATPARA causes transient increase in calcium and therefore, concomitant use of NATPARA and cardiac glycosides (e.g., digoxin) may predispose patients to digitalis toxicity if hypercalcemia develops. Digoxin efficacy is reduced if hypocalcemia is present. In patients using NATPARA concomitantly with digoxin, carefully monitor serum calcium and digoxin levels, and patients for signs and symptoms of digoxin toxicity. Adjustment of digoxin and/or NATPARA may be needed. No drug-drug interaction study has been conducted with digoxin and NATPARA.

Parathyroid hormone (Approved 2015)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125511s004lbl.pdf
Preliminary survey of 49 novel BLAs from May 2010 – May 2017

- **13 (25%)** have dedicated studies
- **19 (39%)** used population pharmacokinetics (popPK) for no interaction claim (Information found in BLA reviews)

<table>
<thead>
<tr>
<th>Category</th>
<th>Cytokines</th>
<th>Growth factors</th>
<th>Enzymes</th>
<th>Monoclonal antibodies</th>
<th>Miscellaneous</th>
<th>Total [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedicated studies [n]</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Some description [n]</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>13</td>
<td>6</td>
<td>35 (46%)</td>
</tr>
<tr>
<td>No information [n]</td>
<td>2</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>Total [n (%)]</td>
<td>11 (14%)</td>
<td>10 (13%)</td>
<td>17 (22%)</td>
<td>29 (38%)</td>
<td>9 (12%)</td>
<td>76 (10%)</td>
</tr>
</tbody>
</table>

Clin Pharmacokinet. 2010 May;49(5):295-310
Pro-inflammatory Cytokine or Cytokine Modulator

TP Intended to be Used in Combination with a Drug

Known Mechanism or General Concern not Related to CYPs or Transporters
Cytokine Effects on CYP450

• IL-1, IL-2, IL-6, IL-10, TNF, IFN

• Some pro-inflammatory cytokines down-regulate CYP levels and decrease clearance resulting in increased exposures

• Reversal of CYP down-regulation in disease states with inflammation or infection by cytokine modulators:
  – In RA, simvastatin exposure was 4-10 fold higher than in healthy
  – 1 week tociluzimab therapy decreased exposure by 57%
  – Sim exposure increased after discontinuation of tociluzimab

Pro-inflammatory Cytokine or Cytokine Modulator

Label Potential for Interaction

In Vitro Study (TP→D) and Label

In Vivo Study (TP→D) – Cocktail or Individual Study

TP Intended to be Used in Combination with a Drug

Known Mechanism or General Concern not Related to CYPs or Transporters
Drug Interaction Studies

Drug interaction studies have not been conducted with DUPIXENT.

7.3 Interactions with CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, TNFα, and IFN) during chronic inflammation. Thus, DUPIXENT, an antagonist of IL-4 receptor alpha, could modulate the formation of CYP450 enzymes.

Therefore, upon initiation or discontinuation of DUPIXENT in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

Dupilumab - IL-4 receptor antagonist. Approved 2017
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf
Is Labeling Without Study Appropriate?

• Most DDIs observed based on cytokine modulation have <2 fold change
  – Not all have been studied

• Specific dose adjustments are not proposed for various substrates for the TP as a perpetrator.

Is there a need to know the exact magnitude of effect?
In Vitro Studies

• Limited use of in vitro methods for TP DDI assessment

• Limitations in predictive value of the models

Ustekinumab- human IL-12 and -23 antagonist approved 2009.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125261s114lbl.pdf

Challenges in Designing Dedicated In Vivo DDI Studies

• Healthy volunteers are mostly inappropriate due to disease-specific differences

• Disease type, disease severity, timing during therapy - level of CYP activity?

• Long half-life = parallel design and long duration of study

• Limited applicability of in vitro evaluations – which CYPs to evaluate – Cocktail study?
Cocktail Study - Daclizumab

- Cocktail Probes: Midazolam (CYP3A), S-Warfarin (CYP2C9), Omeprazole (CYP2C19), Caffeine (CYP1A2) and Dextromethorphan (CYP2D6)

- No effect observed of TP on probes

Daclizumab Interleukin-2 receptor blocking antibody – Approved 2016
PPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761029s001lbl.pdf
Review: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761029Orig1s000ClinPharmR.pdf
Pro-inflammatory Cytokine or Cytokine Modulator

TP Intended to be Used in Combination with a Drug

In Vivo Study (TP→D) and (D→TP) – Crossover, Parallel or Pop PK

Label Results and Management Strategies, if Needed

Known Mechanism or General Concern not Related to CYPs or Transporters
INDICATIONS AND USAGE

ANTHIM® is a monoclonal antibody directed against the protective antigen of Bacillus anthracis. It is indicated in adult and pediatric patients for treatment of inhalational anthrax due to B. anthracis in combination with appropriate antibacterial drugs and, for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate. (1.1)

Drug Interaction Studies

Ciprofloxacin

In an open-label study evaluating the effect of ciprofloxacin on obiltoxaximab PK in healthy adult male and female subjects (study 3), the administration of 16 mg/kg ANTHIM IV infusion prior to ciprofloxacin IV infusion or ciprofloxacin oral tablets twice daily did not alter the PK of obiltoxaximab. Likewise, obiltoxaximab did not alter the PK of ciprofloxacin administered orally and/or intravenously [see Drug Interactions (7.1)].
Population PK

• PopPK used to assess as victim or perpetrator

• PK for the drug of interest (usually available for the TP)

• Dosing and timing (dose and sampling) records are critical for assessment

• Pre-specification of the plan is needed to allow for appropriate data collection

Dedicated Studies - Dulaglutide (T2DM)

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>PK</th>
<th>Ratio and 90%CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>AUC</td>
<td></td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Glucagon-like peptide 1 receptor agonist for Type 2 Diabetes Mellitus
Slows gastric emptying – tested with a variety of oral drugs

Dulaglutide GLP-1 receptor agonist - Approved 2014
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125469s007s008lbl.pdf
Palifermin

• Palifermin is a recombinant KGF, a heparin-binding member of the FGF family

• The original 2004 BLA review stated:
  – Palifermin is bound to heparin in vitro
  – Recommend saline instead of heparin to flush IV
  – LMW heparin should be evaluated because it was used in the clinical setting
# Palifermin + Heparin

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>PK GMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial 1 (HV)</strong>&lt;br&gt;N=30 (3:2) &lt;br&gt;27 evaluable</td>
<td>Pal 60 µg/kg on Day 1 + unfrac heparin</td>
<td>5-fold ↑ in palifermin AUC ↔ aPTT</td>
</tr>
<tr>
<td></td>
<td>Pal 60 µg/kg on Day 1</td>
<td></td>
</tr>
<tr>
<td><strong>Trial 2 (HV)</strong>&lt;br&gt;N=44 &lt;br&gt;(20:16:8) &lt;br&gt;31 evaluable</td>
<td>Pal 40 µg/kg on Days 1-3 + continuous unfrac heparin</td>
<td>425% ↑ in palifermin AUC ↔ Ki67 expression</td>
</tr>
<tr>
<td></td>
<td>Pal 40 µg/kg on Days 1-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No treatment (control)</td>
<td></td>
</tr>
</tbody>
</table>

Take Home Messages

• TP-DDIs have been assessed for:
  – Cytokine/cytokine modulators
  – Drugs used in combination
  – Common concomitant medications (Pop PK)
  – Suspected mechanism other than CYP/transporter related

• DDIs have been observed for pro-inflammatory cytokine and cytokine modulators
  – <2 fold in most cases
  – Can vary based on multiple factors including disease state, severity
Take Home Messages

• DDIs have been observed for a few TPs based on other mechanisms (Palifermin)

• TP-DDI assessment strategies have included:
  – Labeling w/o study for cytokine & cytokine modulators
  – Use of dedicated DDI studies
  – Use of Population PK for DDI assessment
Antibody-Drug Conjugates (ADCs)

• Mab, linker and small molecule (payload)

• Consider both the TP (earlier discussion) and the small molecule

• Same payload in various ADC’s – share info?

Not specifically discussed in DDI guidance
DDI Assessment for ADCs

• In vitro studies for payloads in ADCs

• Dedicated in vivo studies

• Population PK analyses
## ADCs

<table>
<thead>
<tr>
<th>ADC</th>
<th>Payload</th>
<th>DDI of payload</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADO-TRASTUZUMAB EMATANSINE</td>
<td>DM1</td>
<td>• CYP3A substrate&lt;br&gt;• Not inh/ind of major CYPs&lt;br&gt;• No in vivo study</td>
<td>Avoid strong Inhibitor OR delay ADC dose for 3 T1/2 of inhibitor</td>
</tr>
<tr>
<td>BREN'TUXIMAB VEDOTIN</td>
<td>Monomethyl auristatin E (MMAE)</td>
<td>• CYP3A and Pg-P substrate, and CYP3A inhibitor, in vitro&lt;br&gt;• Keto ↑ MMAE 34%&lt;br&gt;• Rifampin ↓ MMAE 46%&lt;br&gt;• ADC ↔ midazolam</td>
<td>Caution with strong CYP3A or PgP inhibitor</td>
</tr>
<tr>
<td>*GEMTUZUMAB OZOGAMICIN</td>
<td>Calicheamicin</td>
<td>? several metabolites in vitro</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Withdrawn from the market
Source of information is PPIs
Challenges in DDI of ADCs

• Payloads generally do not have a wide therapeutic range

• Generally low levels of payload in plasma

• Management strategy
  – Specific dose adjustment is challenging as dosing is based on the ADC
  – Which moiety drives the E-R relationships?
ADCs Take Home Messages

• ADCs- may need to consider both the TP and the payload for DDI assessment

• DDI assessment is important due to the toxicity of the payload

• However, it is difficult to recommend dose adjustments for DDIs
Outstanding Issues

• Is DDI evaluation is needed for TPs?

• Is evaluation for pro-inflammatory cytokine modulators necessary, and if so, what are the design considerations (i.e., the population)?

• Is it appropriate or informative to label potential DDIs without study?
TP DDI: Important not Important

WHERE ARE WE

Now?