Drug interactions of cytokines and anti-cytokine therapeutic proteins

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Early Development, Clinical Pharmacology
Amgen Inc., Seattle WA
The trilogy of commonly observed indirect TP-DDIs


Abuqayyas L, Balthasar, JP. Pharmacokinetic mAb-mAb interaction: anti-VEGF mAb decreases the distribution of anti-CEA mAb into colorectal tumor xenografts. AAPS J 2012 ;14: 445-55.
Outline

• P450 Suppression by Inflammation
  • Tocilizumab: Simvastatin Interaction
  • Nonclinical Studies in Human Hepatocytes
  • Genomics Aspects & Biomarkers
    • C-reactive protein

• Clinical Experience

• Conclusion
P450 Suppression and Normalization

- Small molecule clearance can be modified by Inflammation
- Inflammation can be modified by anti-cytokine mAbs
- Thus anti cytokine mAb can modify small molecule clearance mechanisms
- **Drug-Disease Interaction!**

# How Big is De-suppression? B
tocilizumab (anti-IL6R) Effects on Simvastatin

<table>
<thead>
<tr>
<th>Perpetrator</th>
<th>Victim</th>
<th>AUC before</th>
<th>AUC after</th>
<th>Ratio (fold decrease)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab (10 mg/kg)</td>
<td>Simvastatin</td>
<td>100%</td>
<td>43%</td>
<td>2.3*</td>
<td>Schmitt et al., Clin Pharmacol Ther 2011; 89 735-40,</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Simvastatin</td>
<td>17.3</td>
<td>2.4</td>
<td>7.2</td>
<td>Kyrklund et al., Clin Pharmacol Ther 2000; 68:592</td>
</tr>
</tbody>
</table>

*DDI label language in Tocilizumab (Actemra™) Label

P450 de-suppression is smaller in magnitude than induction by Rifampicin
Effect should be no larger than the CI difference between diseased and healthy subjects!

Other DDI Studies: Omeprazole/CYP2C19 (88% PM & IM, 72% EM), Dextromethorphan /CYP2D6 No significant change

Modified from
Slatter, NBC 2011
Tocilizumab–Simvastatin DDI Triggered Significant Regulatory Interest in TP-SM DDI assessment

2008: Tocilizumab Clinical DDI
“Plasma concentrations of simvastatin were higher in RA patients prior to RoActemra/Actemra administration than those reported for healthy volunteers.” (~50% reduction)

2009: Ustekinumab Approval Letter
“Conduct an in vitro study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes…”

2009-12: Numerous similar requests all across the industry

Primary Hepatocyte Models for Investigating Drug Interactions with Cytokine Modulating Biologics

(Leslie Dickmann and Sonal Patel, PKDM)
General Experiment Design for P450 Suppression by Cytokines in Primary Hepatocytes

Day 1
Plate Hepatocytes
Overlay with Matrigel

Change Media and Replenish cytokine daily

Days 2&3
mRNA Assessment
- P450, UGT, and drug transporter RNA expression using real-time PCR

Viability Assessment
- ATP levels (CellTiter-Glo)
- Trypan Blue exclusion vs untreated cells

Days 4-6
P450 Activity Assessment
- Phenacetin/Testosterone probe substrates for CYP1A2 and CYP3A4 activity

Cytokine Assessment
- APR Markers (CRP, SAA mRNA), select cytokine, cytokine receptor measurements
Cytochrome P450 mRNA was Globally Suppressed by IL-6

Physiological serum [IL-6]*

EC_{50} values allows rank ordering of isoform sensitivity
- CYP3A4 ≥ CYP2B6 > CYP3A5 = CYP2C19 > CYP2C9 >> CYP1A1

*IL-6 serum data from 7 published clinical studies
An Anti-IL6 Monoclonal Antibody is Able to Partially Block CYP3A4 Suppression by IL-6

Dashed red lines = normal range of serum IL-6 (ca. 0.5-100 pg/mL)

All previous literature studies were done at supra-physiological IL-6 concentrations
In Vitro Hepatocyte Studies on IL-6: A mechanistic understanding of the biology

Hepatocytes are OK for measuring direct effects of a single or subset of cytokines, but oversimplify in vivo inflammation

Draft DDI Guidance (2012): “In vitro or animal studies have limited value in the qualitative and quantitative projection of clinical interactions”
Clinical Literature: IL-6 and C-reactive Protein Inversely Correlate with CYP3A Activity after Surgery and in Cancer Patients

Metabolism of erythromycin inversely correlated with plasma IL-6

Metabolism of erythromycin inversely correlated with CRP in cancer patients


Genomic Clues to Mechanism and Predictive Biomarkers?

- GWAS Study by Rosetta Inpharmatics (Merck)
  - 466 human liver samples from multiple centers
  - Gene expression analysis for > 30,000 genes
  - P450 marker activity for 389 livers
  - Genotyping using Affymetrix 500K SNP array

Yang X et al., Genome Research 2010 Aug;20(8):1020-36
Genomic Correlation Between P450s and Acute-Phase Response in 487 Human Liver Donors

Turquoise module is significantly positively correlated with mRNA expression and activity of most P450 genes and contains the majority of P450 genes and P450 regulators.

Pink and brown modules were negatively correlated with most P450s. The pink module was highly enriched for acute phase inflammatory genes.

Modified After: Figure 3 in Yang X et al., Genome Research 2010 Aug;20(8):1020-36
CYP3A4 mRNA Expression Correlates with PXR and CRP mRNA in 487 Human Liver Donors*

Inflammation in the liver subtly disregulates elements of steroid and lipid homeostasis

Plots from GWAS data at sagebase.org from: Yang X et al., Genome Research 2010, 20, 1020-36
Thanks to Dr. Yudong He (CBSS)
Plasma C-reactive Protein as a Population Biomarker for P450 Effects in Inflammation DDI?

- **IL-6 in human liver**
  - Multiple functions
    - Apoptosis, APR, regeneration
  - Drives CRP secretion into plasma (IL-1β too)
  - Drives CYP3A effects relative to IL-1β

- **C-reactive protein**
  - Non specific indicator of inflammation
  - Wide dynamic range
  - Made primarily in liver
  - Half life 5-7 h
  - Pentraxin APR protein that opsonizes bacteria and apoptotic cells for clearance via complement and FcyR-mediated cytosis
  - Inexpensive
  - Normal Ranges (mg/L)*
    - Median 0.8
    - 90th percentile <3
    - 99th percentile <12

*Genetic variants known that can alter CRP response and baseline

Dickmann LJ et al., Current Drug Metabolism. 2012, 13, 930-7

Slatter NBC 2012
CRP Values in Inflammatory Disease Differ by Disease State and Drug Treatment!

Modified after Slatter NBC 2012

Note that C-reactive protein secretion is a direct hepatic response to IL-6 in the liver and data are inherently variable within patient groups (not shown)

Mean or Median C-Reactive Protein (mg/L)

ULN = 3 (90th %)


*Values estimated from graphical or textual data
Clinical Experience:
Therapeutic Protein DDI Study: Tocilizumab: Simvastatin DDI in 12 RA patients

Study design highlights all the key elements that differ from SM DDI studies:

1. PK of simvastatin & β-OH-simvastatin over 24 h
2. PK & PD (IL-6, sIL-6R, CRP) of TCZ over 2 months


## Conclusions

<table>
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<th>Tools</th>
<th>Conclusion</th>
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<tr>
<td>Human Hepatocytes in vitro</td>
<td>• In vitro studies are interesting, but not “actionable” for label making or go/no go clinical study decisions</td>
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<tr>
<td>Potential Human Biomarker</td>
<td>• Human genomic and related data suggests a relationship between CRP and CYP3A suppression</td>
</tr>
<tr>
<td>Disease Effect Magnitude</td>
<td>• How big is the difference in CYP3A status in a disease population relative to a matched healthy population (for RA, psoriasis, UC, Crohn’s etc)?</td>
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<tr>
<td>Clinical Studies</td>
<td>• Clinical Study may be needed until more “no effect” studies on diverse targets and in diverse indications are published</td>
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References:

Dickmann LD, Patel SK, Rock DA, Wienkers LC, Satter JG. “Effects of Interleukin-6 (IL-6) and an anti-IL-6 Monoclonal Antibody on Drug Metabolizing Enzymes in Human Hepatocyte Culture” Drug Metabolism and Disposition. 39: 1415-22. 2011.


Dickmann LJ, McBride HJ, Patel SK, Miner K, Wienkers LC, Satter JG. 2012. Murine collagen antibody induced arthritis (CAIA) and primary mouse hepatocyte culture as models to study cytochrome P450 suppression. Biochemical Pharmacology. 83 1682-89.

Dickmann LJ, Patel SK, Wienkers LC, Satter JG. 2012. Effects of Interleukin 1β (IL-1β) and IL-1β/Interleukin 6 (IL-6) Combinations on Drug Metabolizing Enzymes in Human Hepatocyte Culture. Curr Drug Metab. 13:930-7.