Clinical Pharmacology Considerations

• Mechanistic understanding
  – Drug Metabolism
  – Transporters
  – Genetic variation

• Leveraging pharmacokinetic information
  – Exposure-Response analysis
Drug Metabolism and DILI

- Liver is a major organ exposed following oral administration
  - Generally drug metabolism leads to detoxification
  - Drug/metabolite exposure to liver is a critical factor in predicting risk of DILI
  - Formation and accumulation of reactive metabolites may lead to hepatotoxicity

- Drugs with significant hepatic metabolism (>50%) have a higher likelihood of being associated with hepatic adverse events

Role of CYPs

- Drugs metabolized by CYP1A2, 2C8/9, 3A4/5 may be more likely be associated with DILI risk
- CYP inhibitors when administered at high daily doses as associated with DILI risk

Yu et al. DMD:2:744–750, April 2014
Reactive Metabolites

- Reactive metabolites can reduce hepatic functions resulting in build up of toxic substrates
- Adducts of reactive metabolite and hepatocellular proteins can mediate immune response
- Reactive metabolites can lead to depletion of GSH resulting oxidative stress
  - Dose dependency
Acetaminophen Induced Hepatic Necrosis

- Acetaminophen
  - CYP
  - NAPQI (reactive metabolite)
- Overdose
- Glutathione depletion, covalent binding, hepatotoxicity

Metabolism

- Glucuronide sulphate

Bio-inactivation

- Glutathione conjugation

Hepatic Transporters and DILI

Corsini and Bortollini. JCP: Vol 53 No 5 (2013)
Role of Hepatic Transporters

Inhibition of hepatic transporter proteins is most likely mechanism for cholestatic forms of DILI resulting from accumulation of cholephilic compounds

- Troglitazone - inhibition of OATP1B1/B3 and BSEP
- Pravastatin – inhibition of MRP2
- Bosentan – inhibition of BSEP
Genetic Variation and DILI

- Genetic variation can be a key susceptibility factor for DILI
  - NAT2: isoniazid and sulphonamides
  - UGT1A1: irinotecan, indinavir and ketoconazole
  - UGT2B7, CYP2C8 and ABCC2: diclofenac
  - HLA-I and HLA-II: amoxicillin/clavulanate
  - HLAB*5701: flucloxacillin
Exposure-Response (ER)

- There appears to be a relationship between daily doses of oral prescription drugs and DILI.
- The dose dependency seems to be pronounced along with other predictors such as CYP inhibitors or drug lipophilicity.
- Evaluation of the relationship between drug exposure and markers of hepatocellular injury can be useful for assessing DILI risk.
  - Leverage late phase long-term treatment information.
  - Assumes systemic drug levels a surrogate of exposure in the hepatocyte.
Example 1: Trabectedin

- Indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received prior anthracycline-regimen
- USPI has Warning for Hepatotoxicity and requires assessment of liver function prior to each administration and manage elevated liver function tests with treatment adjustment
- Incidence of DILI was 1.3%
Elevation of ALT and bilirubin exposure dependent

AUC breakpoint (48 ng*hr/mL) obtained by CART analysis

Dose range: 0.024-1.8 mg/m²
From 12 phase 1 & 2 studies
N= 709

Probability of patients with ALT Grade 3 (%)

Steady-state AUC (ng*hr/mL)

Dose: 0.03 – 18 mg/m²

Probability of Bilirubin Toxicity Grade 1+

Steady-state AUC (ng*hr/mL)

Logistic regression
Observed proportion (95% CI)

p < 0.0001
Odds Ratio: 1.6 (95% CI: 1.3-1.9)

Clinical Pharmacology Review for NDA 22447
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207953Orig1s000ClinPharmR.pdf
Example 2: Solithromycin

• NME, ketolide class, seeking approval for community acquired bacterial pneumonia
• Increased incidence of ALT elevations compared to control arm observed in the Phase 3 studies
• No Hy’s Law cases (N = 920)
• Quantitative Structure Activity Relationships show 85% similarity in structure to telithromycin and that hepatotoxicity would be expected with solithromycin use
Incidence of ALT elevation seems exposure dependent

<table>
<thead>
<tr>
<th>Study CE01-300</th>
<th>Study CE01-301</th>
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</thead>
<tbody>
<tr>
<td><strong>ALT elevation</strong>*</td>
<td>Solithromycin Oral</td>
</tr>
<tr>
<td></td>
<td>n/N (%)</td>
</tr>
<tr>
<td>≥ 3×ULN</td>
<td>22/412 (5.3%)</td>
</tr>
<tr>
<td>≥ 5×ULN</td>
<td>7/412 (1.7%)</td>
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</tbody>
</table>

* ALT measured at baseline (Day -1 or 1), Days 4, 7 and 12-17.

- **Phase 1**: Dose escalation studies in phase 1 identified ALT elevation as a dose limiting factor
- **Phase 3**: Overall higher daily exposure and longer treatment in CE01-301 vs CE01-300

* FDA Advisory Committee Presentation for NDA 209006 & 209007 on Nov 4, 2016
  [https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM528873.pdf](https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM528873.pdf)
Incidence of ALT elevation is exposure dependent

FDA Advisory Committee Presentation for NDA 209006 & 209007 on Nov 4, 2016
Conclusion

• DILI is generally considered idiosyncratic
• Careful clinical pharmacology considerations can help in better understanding and predicting DILI risk
  – Drug Metabolism
  – Involvement of Transporters
  – Genetic Variations
  – Exposure-Liver function relationships
Acknowledgements

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