DILI: Clinical Pharmacology Considerations for Risk Assessment

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Drug-Induced Liver Injury (DILI) Conference XVII
June 06, 2017

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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

<table>
<thead>
<tr>
<th>Classifications</th>
<th>DILI positives</th>
<th>DILI negatives</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP Substrates</td>
<td>149</td>
<td>19</td>
<td>3.99 (2.07-7.67)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>No</td>
<td>57</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP Inhibitors</td>
<td>93</td>
<td>16</td>
<td>1.65 (0.85-3.18)</td>
<td>0.1372</td>
</tr>
<tr>
<td>No</td>
<td>113</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP Inducers</td>
<td>43</td>
<td>7</td>
<td>1.55 (0.65-3.68)</td>
<td>0.3246</td>
</tr>
<tr>
<td>No</td>
<td>163</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

- Reactive metabolites can reduce hepatic functions resulting in a build up of toxic substrates
- Adducts of reactive metabolite and hepatocellular proteins can mediate immune response
- Reactive metabolites can lead to depletion of glutathione resulting in 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 Efflux Transporters

Inhibition of hepatic efflux transporters is the 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

Drug Metab Dispos. 2004;32(3):291–294
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 and DILI

• 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 are 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
- US Package Insert has Warning for Hepatotoxicity and requires assessment of liver function prior to each administration and management of elevated liver function tests with treatment adjustment
- Incidence of DILI was 1.3%
Elevation of ALT and bilirubin are exposure dependent

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

Dose range: 0.024-1.8 mg/m²
13 clinical studies (N=713)

Dose: 0.03 – 18 mg/m²
From 12 phase 1 & 2 studies
N=709

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 (QSAR) 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></th>
<th>Study CE01-300</th>
<th>Study CE01-301</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solithromycin Oral n/N (%)</td>
<td>Moxifloxacin Oral n/N (%)</td>
</tr>
<tr>
<td>≥ 3×ULN</td>
<td>22/412 (5.3%)</td>
<td>15/423 (3.5%)</td>
</tr>
<tr>
<td>≥ 5×ULN</td>
<td>7/412 (1.7%)</td>
<td>5/423 (1.2%)</td>
</tr>
</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
Exposure - ALT elevation relationship

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

• Jeffry Florian

• Clinical Pharmacology Review Teams
  – NDA 207953 (Trabectedin)
  – NDA 209006 & 209007 (Solithromycin)