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Modeling for Susceptibility Factors: The Case Study with Troglitazone

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Troglitazone (TGZ)

- First in thiazolidinedione class; PPARγ agonist
  - Reduces hepatic and peripheral insulin resistance
  - Approved for the treatment of type II diabetes

- Hepatotoxicity
  - Hepatotoxicity was not detected in preclinical studies
  - 2% of patients developed ALT elevations >3X ULN in clinical trials
  - Withdrawn from the market due to idiosyncratic hepatotoxicity
Mechanisms of TGZ Hepatotoxicity Unknown

DILI

- Mitochondrial dysfunction
- Oxidative stress
- Induction of apoptosis
- Inhibition of bile acid transport
- Reactive metabolite

Chojkier M (2005) Hepatology
Bile Acid

Physiology
• Promote lipid absorption
• Signaling molecules activating nuclear receptors

Pathophysiology
• Mitochondrial toxicity

Hydrophilic, less cytotoxic
Hydrophobic, cytotoxic
Mechanisms of DILI: Transport Protein-Mediated Bile Acid-Drug Interaction

Hepatotoxicity

BSEP (Bile Salt Export Pump);
NTCP (Sodium-Taurocholate Cotransporting Polypeptide);
MRP (Multidrug Resistance–Associated Protein);
OST (Organic Solute Transporter)

TGZ: troglitazone
TS: troglitazone sulfate
Bile acid transport inhibition demonstrated in *in vitro* assays

However, the relationship between bile acid transport inhibition and *in vivo* hepatotoxicity has not been evaluated

Mechanistic, Multi-scale Modeling
DILIsym®

• A predictive, mechanistic, mathematical model of DILI
• Represents drug disposition and the biochemical/physiological processes involved in hepatotoxicity
• Middle-out, multi-scale approach
• Organized into various smaller sub-models

- Reactive metabolite-based hepatotoxicity
- Mitochondria toxicity
- Bile acid transport inhibition/bile acid toxicity

Hepatotoxic potential of TGZ in humans?

Adapted from www.dilisym.com
Bile Acid Transport Inhibition Module

Drug PBPK Model
- Bile Acid Transport Inhibition
- Inhibition of ATP Synthesis
- Increased Cell Death Rate

Bile Acid Homeostasis Model

Cellular ATP Model

Hepatocyte Life Cycle Model

Biomarker Model

Yang et al. in preparation
Bile Acid Transport Inhibition Module

Drug PBPK Model

Bile Acid Transport Inhibition

Bile Acid Homeostasis Model

Inhibition of ATP Synthesis

Cellular ATP Model

Increased Cell Death Rate

Hepatocyte Life Cycle Model

Biomarker Model

Inhibition constants (i.e., $K_i$, $IC_{50}$) measured in vitro

Yang et al. in preparation; Woodhead et al. CPT:PSP, in revision
What are the intracellular bile acid concentrations that cause ATP depletion?

Bile Acid Transport Inhibition Module

Drug PBPK Model

Bile Acid Homeostasis Model

Cellular ATP Model

Hepatocyte Life Cycle Model

Biomarker Model

Inhibition of ATP Synthesis

Increased Cell Death Rate

Yang et al. in preparation; Yang et al. Tox Sci, in submission

Howell et al. (2012) J Pharmacokinet Pharmacodyn
Bile Acid Transport Inhibition Module

Drug PBPK Model

Bile Acid Homeostasis Model

Inhibition of ATP Synthesis

Cellular ATP Model

Increased Cell Death Rate

Hepatocyte Life Cycle Model

Biomarker Model

Quantitative relationships between intracellular bile acid concentrations and ATP levels were determined using \textit{in vitro} data.

Yang et al. in preparation; Yang et al. Tox Sci, in submission
Bile Acid Transport Inhibition Module

Drug PBPK Model

Bile Acid Homeostasis Model

Cellular ATP Model

Hepatocyte Life Cycle Model

Bile Acid Transport Inhibition

Inhibition of ATP Synthesis

Increased Cell Death Rate

Mature Hepatocytes

Necrotic Hepatocytes

Apoptotic Hepatocytes

Mitotic Hepatocytes

Young Hepatocytes

Biomarker Model

Howell et al. (2012) J Pharmacokinet Pharmacodyn
Bile Acid Transport Inhibition Module

Drug PBPK Model

Bile Acid Homeostasis Model

Cellular ATP Model

Hepatocyte Life Cycle Model

Serum ALT

Hepatocyte Necrotic Flux

Liver ALT

Intermediate ALT

Serum ALT

ALT Clearance

Serum Bilirubin

RBC Bilirubin Release

Plasma Bilirubin

Circulating Unconjugated Bilirubin

Fraction Viable Hepatocytes

Hepatocyte Bilirubin

Average Liver ATP

Glucuronidated Bilirubin

Eliminated Bilirubin

Howell et al. (2012) J Pharmacokinet Pharmacodyn
Population Analysis

• Incidence of TGZ-mediated hepatotoxicity is low
  - 2% of patients experience ALT elevations >3X ULN in clinical trials

• Large inter-individual variability exists in bile acid profile

Population variability needs to be considered in predicting TGZ-mediated hepatotoxicity that involves bile acid transport inhibition

Construction of Sample Population (SimPops™)

Construction of Human Sample Population (SimPops™)

- Drug PBPK Model
  - Bile Acid Transport Inhibition
    - Model Input Variation
      - 1
      - 10
    - TGZ intestinal absorption
    - TGZ hepatic uptake
    - TGZ sulfation
    - TGZ sulfate biliary clearance

- Bile Acid Homeostasis Model
  - Inhibition of ATP Synthesis
    - Model Input Variation
      - 1
      - 10
    - Bile acid uptake
    - Bile acid biliary excretion
    - Bile acid basolateral efflux
    - LCA synthesis in the intestine
    - Bile acid amidation
    - FXR-mediated regulation

- Cellular ATP Model
  - Increased Cell Death Rate

- Hepatocyte Life Cycle Model

Serum ALT (U/L)

Yang et al. in preparation; Woodhead et al. CPT:PSP, in revision
Bile Acid Transport Inhibition Alone Predicted TGZ Hepatotoxicity in Human SimPops™

Simulation Results

HUMAN

Maximum Serum ALT (U/L)

30X ULN

3X ULN

Simulated DILI responses in human SimPop™ (n=331) administered 200, 400, or 600 mg/day TGZ for 6 months
## Bile Acid Transport Inhibition Alone Predicted TGZ Hepatotoxicity in Human SimPops™

### Simulation Results & Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Simulations</th>
<th>Clinical Trials</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TGZ 400 mg (n=331)</td>
<td>TGZ 600 mg (n=331)</td>
</tr>
<tr>
<td>ALT &gt; 3X ULN (%)</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>ALT &gt; 5X ULN (%)</td>
<td>1.2</td>
<td>3.0</td>
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<tr>
<td>ALT &gt; 8X ULN (%)</td>
<td>0.9</td>
<td>2.4</td>
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<tr>
<td>ALT &gt; 30X ULN (%)</td>
<td>0</td>
<td>0.3</td>
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<tr>
<td>Bili &gt; 2X (%)</td>
<td>0.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Jaundice (%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hy’s law (%)</td>
<td>0.9</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*ULN = 34 in the clinical trials

N/A, not available

14 individuals with ALT>3X in simulation of 600 mg TGZ

Simulated DILI responses in human SimPop™ (n=331) administered 200, 400, or 600 mg/day TGZ for 6 months

*Watkins and Whitcomb (1998) NEJM; Yang et al. in preparation*
Mechanistic Model Reasonably Predicted Delayed Presentation of TGZ Hepatotoxicity

**Simulation Results**

*Yang et al. in preparation*

- **Serum ALT (U/L)**
  - 3X ULN
  - 30X ULN

**Time to peak ALT**
- Simulated: 110 ± 62 days
- Clinical Trials: 147 ± 86 days

- Impaired bile acid transport
- Depletion of hepatic ATP
- Inhibition of ATP synthesis
- Hepatic bile acid accumulation
- TGZ
- TS
Susceptibility Factors for TGZ Hepatotoxicity

- TGZ absorption
- TGZ hepatic uptake
- TGZ metabolism
- ↓ TS biliary clearance
- ↓ Bile acid biliary excretion
- ↓ Bile acid basolateral efflux
- Bile acid hepatic uptake
- Bile acid amidation
- Bile acid sulfation
- ↓ FXR-mediated feedback regulation
- ↓ Body weight
- ↑ LCA synthesis in the intestinal lumen

DILI
Conclusions and Perspectives

• Mechanistic modeling based on TGZ-mediated bile acid effects adequately predicted the incidence and delayed presentation of TGZ hepatotoxicity

• Population analysis allowed identification of potential susceptibility factors for TGZ hepatotoxicity

• Mechanistic models that integrate physiological information and experimental data can evaluate DILI mechanisms and may be useful to prospectively predict hepatotoxic potential of new drug candidates
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