Development of a Quantitative Systems Toxicology Model of Drug-Induced Cholangiocyte Injury in DILIsym

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Abstract #2253

INTRODUCTION

- Cholangiocyte injury accounts for a quarter of drug-induced liver injury (DILI) cases and is associated with higher rates of morbidity and mortality than hepatocellular DILI (Chalasani et al., 2015).
- There are currently no methods to screen drugs for cholangiocyte toxicity potential at the lead candidate selection phase.
- Inhibition of multidrug resistance protein 3 (MDR3) by drugs has been shown to correlate with cholangiocyte injury and drug toxicity in humans.
- MDR3 mediates transport of phospholipids to the bile canaliculus. Inhibition of phospholipid transport reduces micelle formation resulting in free bile acids that can damage cholangiocytes.
- Clinically, cholangiocyte injury is defined as an isolated rise in serum alkaline phosphatase.

METHODS

- A Quantitative Systems Toxicology model of drug-induced cholangiocyte injury was built in Matlab (v. R2017b) and incorporated into DILIsym v8A to study the impact of inhibition of MDR3 in conjunction with bile acid kinetics.

Phospholipid Transport
- *Homeostatic transport of biliary phospholipids*
- *Disruption of phospholipid transport upon inhibition of MDR3*

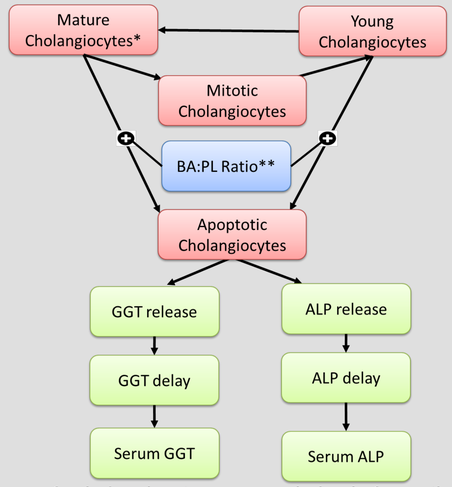
Cholangiocyte Life Cycle
- *Apoptosis and proliferation of cholangiocytes*
- *Effect of an abnormal BA:PL ratio on cholangiocyte death and biomarker release*

Elevation of Serum Biomarkers
- *Homeostatic levels of biomarkers – alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) in serum and liver and their elevation in cholangiocyte injury*

MDR3 Inhibitor Effects Testing
- *Represented model MDR3 inhibitors- itraconazole and fluvoxamine (with and without cholestatic potential respectively) to investigate whether drug-induced change in BA:PL ratio can explain ALP/ GGT increase*

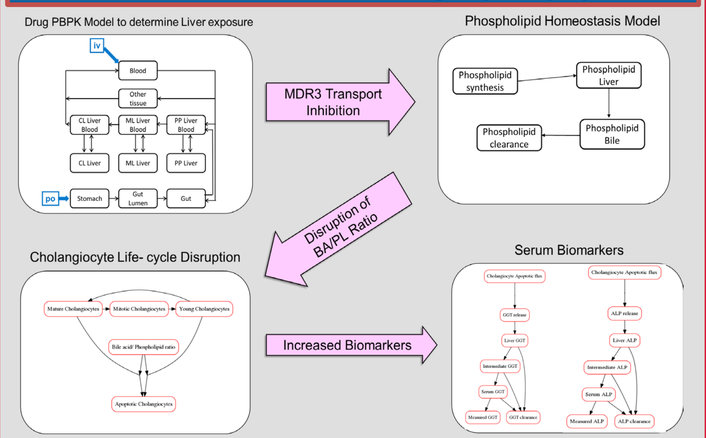
RESULTS

Cholangiocyte Injury Model Outline

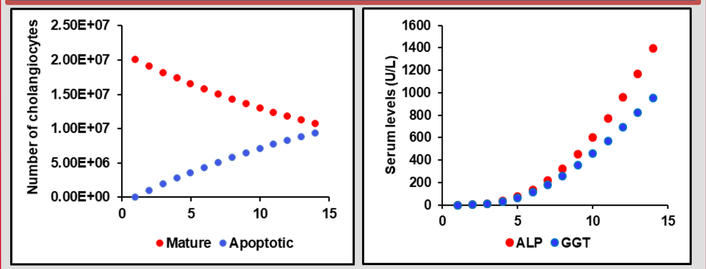


*Cell numbers of cholangiocytes were derived from the following references: Barros 2009, Yoo 2016, Xia 2006.
** BA/PL ratio at homeostasis is believed to be in the range of 8-10 and increases to about 20 after liver transplantation (Gueken 2004). This increase elevates cholangiocyte apoptotic flux which further leads to release of ALP and GGT.

MDR3-Inhibition Mediated Cholangiocyte Injury Model

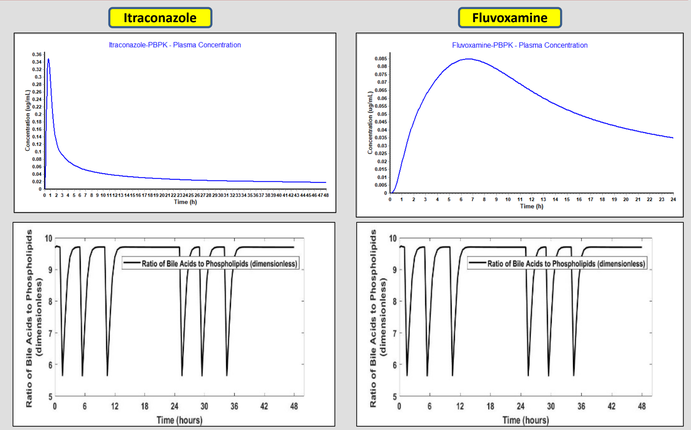


Simulation Results in Baseline Model with Theoretical MDR3 Inhibition



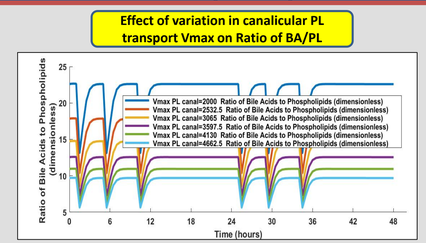
A theoretical MDR3 inhibitor introduced to the cholangiocyte-phospholipid-bile acid system caused disruption in phospholipid transport, leading to increased BA:PL ratio. There was a significant increase in cholangiocyte apoptotic flux, while the number of mature cholangiocytes decreased. Serum ALP and GGT levels increased following a delay as observed in clinical profiles.

Simulation Results with MDR3 Inhibition



Two MDR3 inhibitors were tested in the model: Itraconazole, having DILI liability; MDR3 Ki = 1 uM and Fluvoxamine, with no DILI liability; MDR3 Ki = 5 uM (Aleo, 2017). PB/PK model of these drugs (developed in GastroPlus 9.6) was used to generate blood/ liver concentrations and imported into DILIsym as Specified data (as shown above). Cholangiocyte toxicity was not observed in baseline individual (no elevation in BA/PL ratio) with a single dose of either of these compounds.

Sensitivity Analysis



CONCLUSIONS & FUTURE DIRECTIONS

- Data for changes in BA/PL ratio observed in patients after liver transplantation was leveraged to build a predictive cholangiocyte liver toxicity model via inhibition of MDR3.
- BA/PL ratio is affected by MDR3 expression levels (Meier et al, 2006) as observed in sensitivity analysis.
- This model was used to understand the potential of drug-induced cholangiocyte toxicity of exemplar compounds such as itraconazole.
- For future experimentation,
  - Effect of multiple- dose of exemplar compounds will be simulated in baseline as well as sensitive individuals.
  - A cohort of sensitive individuals will be constructed having variability in bile acid as well as phospholipid transport parameters.

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