Development of a Quantitative Systems Toxicology Model of Multidrug Resistance Protein 3 (MDR3) Inhibition to Predict Bile Acid-Mediated Cholestatic Drug-Induced Liver Injury

AUTHORS

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BACKGROUND

- Multidrug resistance protein 3 (MDR3) translocates phospholipids (PLs) from the inner to the outer leaflet of the canalicular membrane of hepatocytes
- These flopped PLs can form mixed micelles with bile acids (BAs) that have been excreted into the bile canaliculus by the bile salt export pump (BSEP)
- Drug-induced inhibition of MDR3 function can lead to a reduction in PLs available for micelle formation with BAs, resulting in a biliary excess of toxic BA monomers
- Biliary increases in free BAs can damage the bile duct epithelial cells, i.e., cholangiocytes, which may develop into clinically defined cholestatic liver injury
- Cholangiocellular mechanisms that could compensate for biliary BA elevations include the cholehepatic shunt pathway for BAs and the biliary secretion of bicarbonate
- Computational models of drug-induced bile duct injury in humans at the individual and population level, which may aid in the prediction and prevention of drug-induced hepatotoxicity, have thus far been lacking

METHODS

- To predict drug-induced bile duct injury in humans, DILIsym, a quantitative systems toxicology model of drug-induced liver injury (DILI), was extended by representing key features of the bile duct that are believed to impact cholestatic liver injury (**Fig. 1**)
- Representations of PL excretion, modes of MDR3 inhibition, biliary BA toxicity and the compensatory effects of cholehepatic shunting and biliary bicarbonate secretion have been developed
- Publicly available clinical data were used to calibrate and validate a virtual, healthy representative subject and population (n=285)
- Sensitivity analyses were performed for 1) modes of MDR3 inhibition, 2) the cholehepatic shunt pathway, and 3) biliary bicarbonate concentrations
- To further validate the model, population-based simulations were performed with compounds that have established interactions with BA transport and known clinical outcomes

Novel mathematical model of bile acid and phospholipid disposition shows the potential to predict - and provide mechanistic insights into - clinically defined cholestatic liver injury caused by certain drugs

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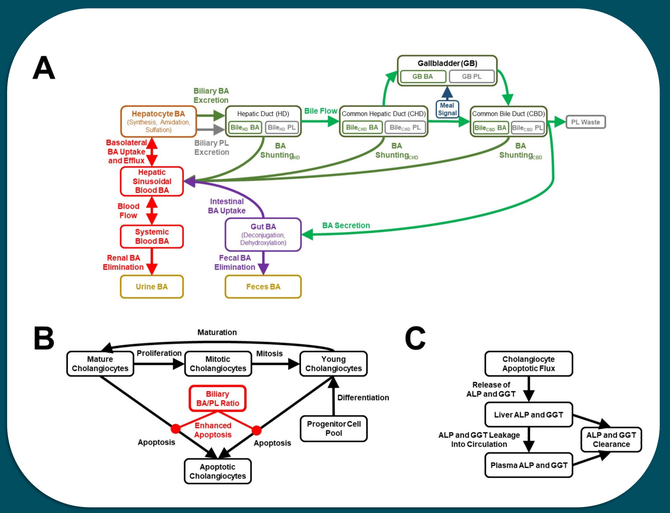

Figure 1. The novel cholestatic liver injury model represents features related to (A) bile acid and phospholipid homeostasis, (B) the cholangiocyte life cycle for each of the three bile duct segments, and (C) cholestatic liver injury biomarkers

RESULTS

- Simulations suggested that non-competitive and mixed inhibition (α=5) of MDR3 has a profound impact on PL efflux and bile duct injury, while competitive inhibition does not (**Fig. 2**)
- Simulations indicated that an enhanced functionality of the cholehepatic shunt decreases the BA burden in the bile duct, but increases BA concentrations in hepatocytes
- The model predicted that increases in biliary bicarbonate concentrations (from 25 to 65 mM) reduces shunting of BAs, but raises the bile flow rate
- The model with its extended representation of BA disposition accurately predicted DILI liability for compounds with known interactions with BA transport
- For instance, virtual population simulations with the DILI exemplars AMG-009, TAK-875 and troglitazone predicted ALT>3x ULN in a subset of simulated subjects, with frequencies consistent with clinical data, while simulations with the clean (no DILI) exemplars ambrisentan and pioglitazone resulted in no clinically relevant biomarker elevations

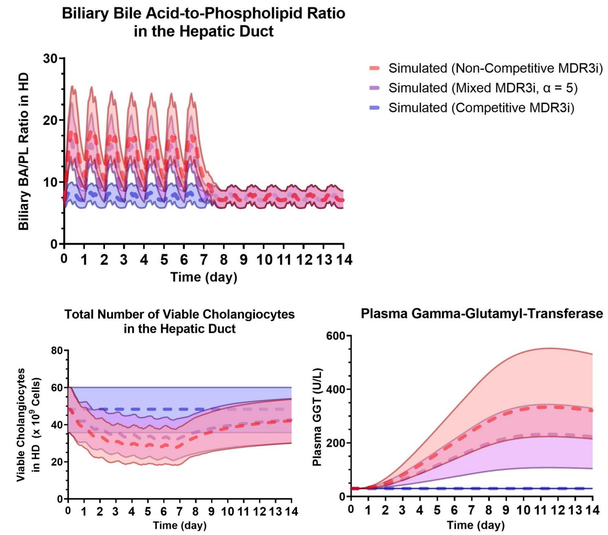

Figure 2. Comparison of non-competitive multidrug resistance protein 3 (MDR3) inhibition, mixed MDR3 inhibition (α=5) and competitive MDR3 inhibition for the biliary bile acid/phospholipid (BA/PL) ratio in the hepatic duct (HD, top panel), viable cholangiocytes in the HD (bottom left panel), and plasma gamma-glutamyl-transferase (GGT, bottom right panel). Dashed profiles indicate the SimPops (n=285) average for the three modes of inhibition, while the 2.5th–97.5th percentiles of the SimPops are depicted by the transparent shading. MDR3i, MDR3 inhibition

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CONFLICT OF INTEREST

JB, KY, JA, GT, SS, BH, and JW are or were employed by Simulations Plus Inc., while PW has no conflicts of interest to disclose.