Quantitative Systems Toxicology (QST) Modeling Using a New Virtual Population in BIOLOGXsym Offers Mechanistic Insights Into Bile Acid-mediated Biologics-induced Liver Injury (BILI) Upon Cimaglermin Alfa (GGF2) Administration

James J. Beaudoin[1], Lawrence A. Vernetti[2], D. Lansing Taylor[2], Albert Gough[2], Lara Clemens[1], Christina Battista[1], Scott Q. Siler[1], Lisl K.M. Shoda[1], Brett A. Howell[1] and Kyunghee Yang[1]

[1]Quantitative Systems Pharmacology Solutions, Simulations Plus Inc., Research Triangle Park, NC, USA;

[2]Drug Discovery Institute, University of Pittsburgh, Pittsburgh, PA, USA

INTRODUCTION

Biopharmaceuticals are increasingly used to treat various medical conditions, but BILI events can end the clinical development of otherwise promising therapies, such as the treatment of heart failure patients with the growth factor protein GGF2. Transient increases in the BILI biomarkers plasma alanine aminotransferase (ALT) and total bilirubin (TB) suspended phase I trials of GGF2, but the mechanism underlying these biomarker elevations was not understood[1,2]. Combining assay outputs from a human biomimetic liver acinus microphysiology system with BIOLOGXsym, a QST modeling platform for macromolecules, representing relevant liver biochemistry and mechanistic effects of biologics on liver pathophysiology, has recently provided mechanistic understanding of GGF2-induced hepatotoxicity[3], and this approach was further investigated in the present work.

RATIONALE AND OBJECTIVE

Previously performed proof-of-concept simulations of intravenously administered GGF2 (1.5 mg/kg) suggested that downregulation of basolateral bile acid transport was the main contributor to plasma ALT elevations in a representative virtual subject in BIOLOGXsym, with a minor role for biliary efflux[3]. It is unclear what the impact of GGF2 is on these pathways at the population level. To obtain new mechanistic insights into bile acid-mediated BILI upon GGF2 administration, an extended bile acid homeostasis representation[4] and a new virtual population with interindividual variability in mechanistic pathways were implemented in BIOLOGXsym simulations. The differential contributions of basolateral (*e.g.*, multidrug resistance-associated protein (MRP) 3/4-mediated) versus biliary (*e.g.*, bile salt export pump (BSEP)-mediated) bile acid efflux pathways were investigated in a representative virtual subject, and in a new cohort of individuals (n=32) that were deemed sensitive to GGF2 hepatotoxicity.

METHODS

Liver Acinus MicroPhysiology System (LAMPS)

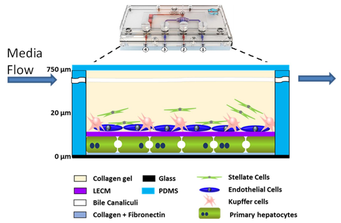

Fig. 1: Schematic diagram of the LAMPS showing the 4 liver cell types (hepatocytes, liver sinusoidal endothelial cells (LSECs), stellate cells, and Kupffer cells) organized into a complex, 3D biomimetic of the human liver.

The LAMPS is an experimental platform that includes multiple liver cell types to model liver diseases and assess drug efficacy and safety. LAMPS recapitulates the structure and function of the liver acinus in a physiologically relevant manner for the evaluation of hepatotoxicity responses to drugs and chemicals[5].

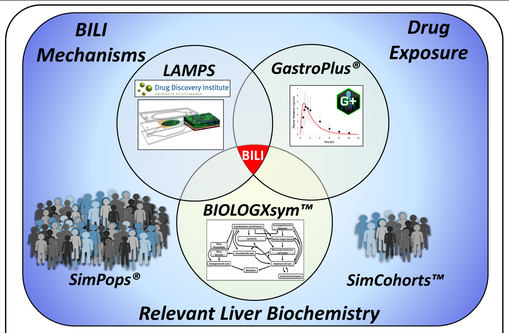

Fig. 2: BIOLOGXsym predicts BILI by intersecting drug exposure, mechanisms, and liver biochemistry. SimPops and SimCohorts are large and small sets of virtual subjects, respectively, allowing for the incorporation of population variability in BIOLOGXsym simulations.

Diagrams of Key Sub-models in BIOLOGXsym for GGF2 Simulations

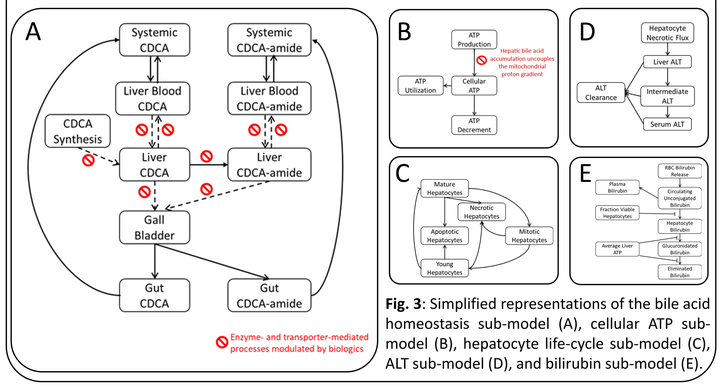

Fig. 3: Simplified representations of the bile acid homeostasis sub-model (A), cellular ATP sub-model (B), hepatocyte life-cycle sub-model (C), ALT sub-model (D), and bilirubin sub-model (E).

RESULTS

Significant Toxicity Findings in LAMPS Chips Treated with GGF2 at 10, 100, and 382 ng/mL

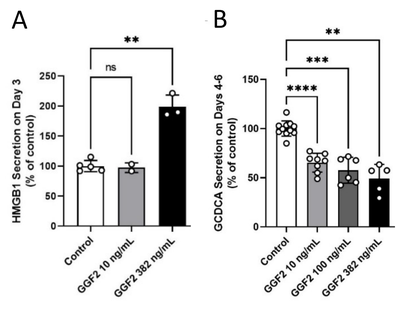

Fig. 4: No overt toxicity in the form of lactate dehydrogenase release was identified in LAMPS, but HMGB1 was significantly elevated at 382 ng/mL GGF2 on day 3 (A). Secretion of GCDCA was significantly decreased on days 4-6 in a dose-dependent manner (B). Values presented as individual LAMPS chips (open circles) and mean ± SD. Statistical significance is indicated by asterisks; ** < 0.01, *** < 0.001, **** < 0.0001. ns, not significant. GCDCA, glycochenodeoxycholic acid; HMGB1, high mobility group box 1.

These GGF2-mediated reductions of bile acid secretion in LAMPS as well as published transcriptional data on GGF2-mediated effects on the regulation of bile acid and bilirubin disposition[6] were used to derive mechanistic toxicity parameters in BIOLOGXsym for GGF2.

Simulations of GGF2-mediated Hepatotoxicity in BIOLOGXsym

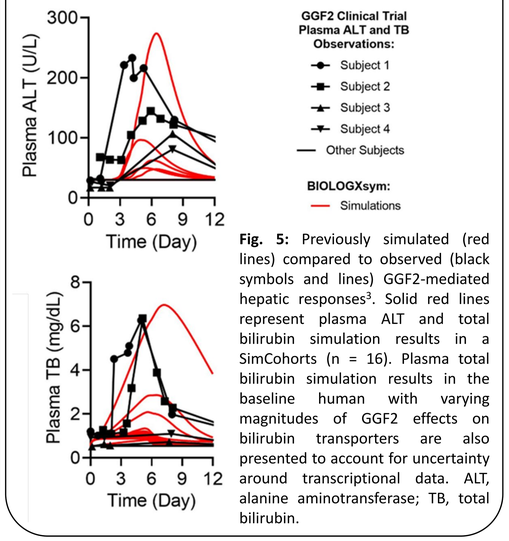

Fig. 5: Previously simulated (red lines) compared to observed (black symbols and lines) GGF2-mediated hepatic responses[3]. Solid red lines represent plasma ALT and total bilirubin simulation results in a SimCohorts (n = 16). Plasma total bilirubin simulation results in the baseline human with varying magnitudes of GGF2 effects on bilirubin transporters are also presented to account for uncertainty around transcriptional data. ALT, alanine aminotransferase; TB, total bilirubin.

BIOLOGXsym Simulation Heatmaps of the Impact of GGF2-mediated Bile Acid Efflux Downregulation on Bile Acid and BILI Biomarker Levels in a Representative Virtual Subject and Sensitive SimCohorts

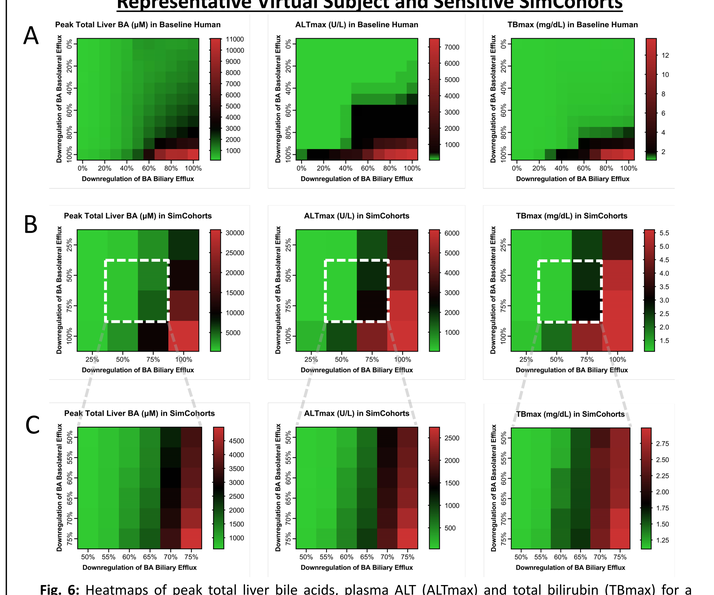

Fig. 6: Heatmaps of peak total liver bile acids, plasma ALT (ALTmax) and total bilirubin (TBmax) for a sensitivity analysis of GGF2-mediated downregulation of bile acid biliary efflux and basolateral efflux. Efflux pathways were downregulated by (A) 0-100% with 10% intervals in a representative virtual subject, (B) 25-100% with 25% intervals in a sensitive SimCohorts (n=32), or (C) 50-75% with 5% intervals in a sensitive SimCohorts (n=32). Green and red squares represent more desirable or detrimental outcomes in bile acid, ALT and total bilirubin levels, respectively. Values presented as individual (A) and mean results (B and C). ALT, alanine aminotransferase; BA, bile acid; TB, total bilirubin.

CONCLUSIONS

- *In vitro* data from LAMPS can be successfully integrated into a QST model to recapitulate BILI liabilities and provide mechanistic explanation for observed clinical liver safety signals.
- Simulations with a representative virtual subject in BIOLOGXsym using an extended bile acid representation continue to support a key role for basolateral bile acid transport downregulation in explaining GGF2-induced ALT elevations.
- However, a more dominant role for the downregulation of biliary bile acid excretion, and subsequent hepatocellular BA accumulation, is predicted at the population level in sensitive individuals.
- In conclusion, population-based simulations in BIOLOGXsym can provide new mechanistic insights into BILI.

REFERENCES

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