Quantitative Systems Toxicology Identifies the Mechanism and Data Gaps for Evaluating the Hepatotoxicity of Compound V

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PURPOSE

Compound V is a small molecule with potential therapeutic benefits in patients with obesity. An early clinical safety trial produced two patients with liver enzyme elevations. Using a combination of *in vitro* assays and *in silico* modeling, **this study investigated whether Compound V is capable of inducing hepatocyte cell death, and if so, what mechanism(s) may be involved and to what extent the compound concentration in the liver plays a role.**

CONCLUSIONS

These results demonstrate the ability for QST modeling, specifically DILIsym, to propose plausible rationales for difficult-to-explain clinical liver toxicity data, and to suggest which further experiments would be most useful for understanding the underlying mechanisms of certain DILI cases.

METHODS

Compound V disposition and potential liver toxicity was modeled using DILIsym, a quantitative systems toxicology (QST) model of drug-induced liver injury, which evaluates compounds based on three major mechanisms of liver cell injury: bile acid (BA) transporter inhibition, mitochondrial dysfunction (including inhibition of the electron transport chain), and production of reactive oxygen species (ROS). *In vitro* assays indicated Compound V had the potential to inhibit BA transporters (including NTCP, BSEP, MRP3, and MRP4), inhibit the protein complexes in the electron transport chain, and produce ROS. A physiologically-based pharmacokinetic (PBPK) model was developed in GastroPlus in order to estimate liver concentration of Compound V.

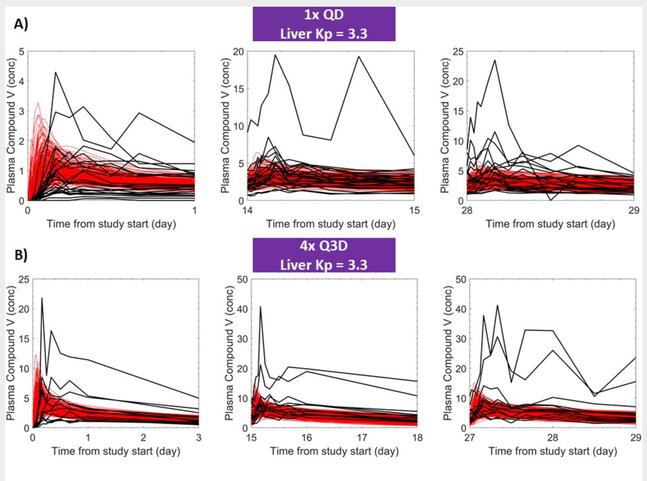

Figure 1: Comparison of population-level PBPK simulations with clinical data. Thin, red lines show the individual simulated plasma exposure of Compound V. Thick, black lines show the same measure in individual clinical volunteers. Both simulated doses used the *in silico* predicted liver Kp value of 3.3.

A) Plots corresponding to a 1x QD dosing regimen. B) Plots corresponding to a 4x Q3D dosing regimen. The PBPK model was optimized to single dose clinical data and validated with the multiple dose clinical data shown here.

RESULTS

Based on the *in vitro* experiment results and the liver exposure predictions, DILIsym predicted that Compound V can injure hepatocytes and produce ALT elevations in some patients. Although Compound V showed toxicity signals in all three *in vitro* assays, mechanistic analysis in DILIsym suggested ROS production is the primary mechanism of injury; specifically, ROS production is both necessary and sufficient to produce cell injury.

Mechanisms Off	Mechanisms On	Simulated ALT >3x ULN Frequency
None	All	15/15
ROS	ETCi, BAi	0/15
ETCi	BAi, ROS	15/15
BAi	ETCi, ROS	15/15
ETCi, BAi	ROS	15/15
BAi, ROS	ETCi	0/15
ETCi, ROS	BAi	0/15

ETCi = electron transport chain inhibition
BAi = bile acid transporter inhibition
ROS = reactive oxygen species generation

Table 1: Mechanistic analysis of Compound V in DILIsym. Simulations of a SimCohort of fifteen individuals with ALT elevations above 3x ULN were repeated with certain hepatotoxic mechanisms turned off or on. These simulations followed the 0.5mg QD dosing regimen using a liver Kp value of 2.4. These results show the ROS toxicity mechanism is both necessary and sufficient to produce the simulated ALT elevations in DILIsym.

This *in silico* prediction of Compound V hepatotoxicity was found to be highly sensitive to the value of the liver:blood partition coefficient (Kp) in the PBPK model. Increases in estimated liver partitioning correspond to higher simulated levels of peak ALT. Because no preclinical measurement of liver Kp was available, our estimates range from 0.33 (based on the *in vitro* intracellular concentration to supernatant ratio) to 3.3 (based on *in silico* prediction from GastroPlus). A SimPops simulation using a Kp value of 2.1 predicted a frequency of ALT elevations in a patient population most similar to the frequency of clinically observed ALT elevations.

Simulated Individuals with ALT >3x ULN		
Liver K_P	1x QD	4x Q3D
0.33	0.00% (0/285)	0.00% (0/285)
1.72	0.00% (0/285)	4.91% (14/285)
2.10	2.46% (7/285)	12.6% (36/285)
2.40	5.26% (15/285)	20.7% (59/285)
3.30	61.4% (175/285)	92.3% (263/285)

Table 2: Summary of SimPops results when varying liver Kp value. The lowest value simulated is the *in vitro* estimation of 0.33; while, the largest value of 3.3 is the *in silico* prediction from GastroPlus. Each SimPops simulation included 285 individuals. Clinically, ALT elevations were only observed (two out of sixteen volunteers) in the 1x QD study; whereas, no ALT elevations were observed in the 4x Q3D study of sixteen volunteers.

Furthermore, the simulations suggested an exposure-response relationship which was not present in the clinic; the two volunteers in the clinical trial with ALT elevations had some of the lowest compound plasma exposure relative to other volunteers. *In silico* predictions with GastroPlus suggested that because Compound V is highly lipophilic, the value of the liver Kp may vary significantly depending on amount of liver fat. DILIsym therefore suggested that the lack of an exposure-response relationship may be due to differences in liver fat among the obese patients in the clinical trial. Future research with obese animal models may be able to confirm or reject this hypothesis.

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