Representation of Efavirenz-mediated Drug-Induced Liver Injury (DILI) Using Quantitative Systems Toxicology (QST)

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Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with other agents to treat human immunodeficiency virus (HIV) infection. Efavirenz treatment is associated with a low frequency of serum enzyme elevations[1]. To understand the hepatotoxicity mechanisms underlying clinically observed liver signals, efavirenz was represented in DILIsym®, a QST model of DILI.

Methods

- The potential for efavirenz to inhibit bile acid transporters was assessed using transporter-overexpressing vesicles and cells.
- The potential for efavirenz to induce mitochondrial dysfunction or oxidative stress was assessed in HepG2 cells.
- Mechanistic *in vitro* data were used to define DILIsym hepatotoxicity parameters for efavirenz.
- A previously constructed GastroPlus physiologically based pharmacokinetic (PBPK) representation[2] was used to predict efavirenz exposure.
- Simulated populations (SimPops) that include variability in hepatotoxicity mechanisms and in efavirenz exposure were used to simulate the *in vivo* response in humans to efavirenz in DILIsym.

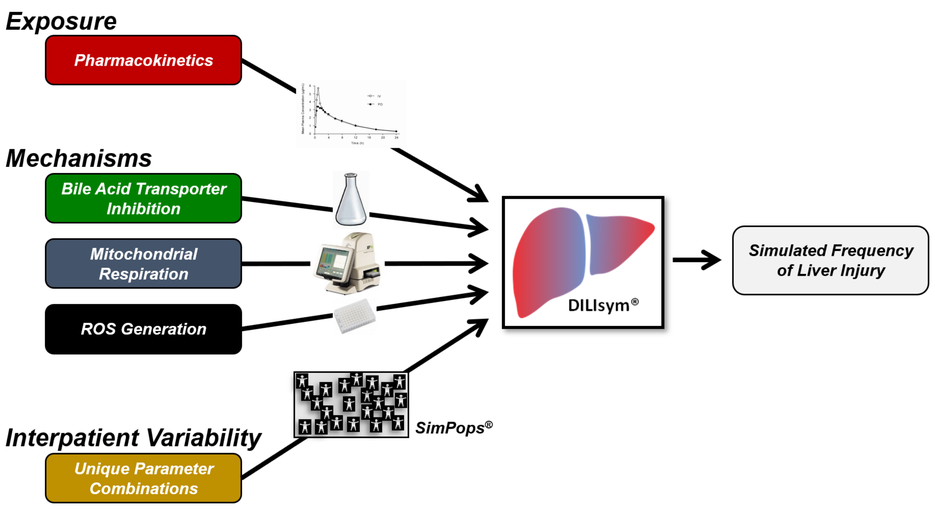

Figure 1. Diagram of the overall workflow for this study, including the processes of determining compound exposure, determining toxicity parameters from *in vitro* data, and incorporating interpatient variability to simulate the frequency of liver injury

Results

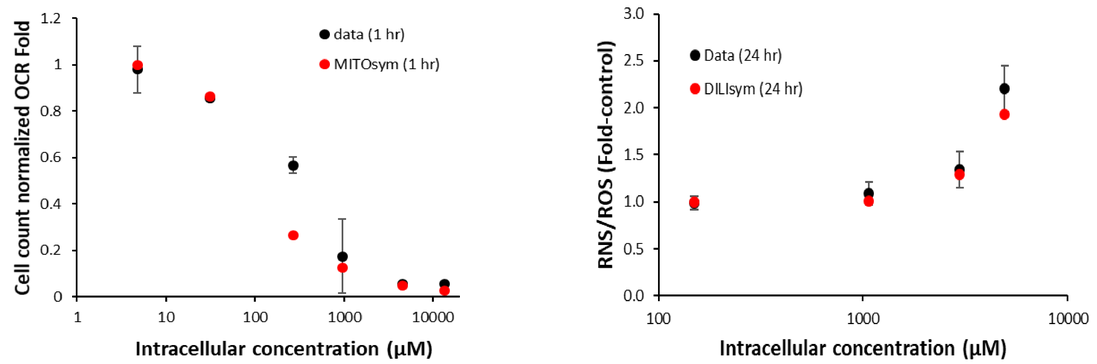

Figure 2. Comparison of simulation results and *in vitro* assay data to identify DILIsym parameter values that reproduce the efavirenz-mediated OCR response at 1 hr (left) and the efavirenz-mediated ROS response at 24 h (right).

- Mechanistic *in vitro* assays indicated that efavirenz inhibits the mitochondrial electron transport chain (ETC), increases oxidative stress, and inhibits bile acid transporters (BSEP, NTCP, and MRP4).
- Combining *in vitro* hepatotoxicity data with predicted exposure, DILIsym predicted infrequent ALT elevations (1-2%) in SimPops following administration of efavirenz (600 mg QD) for 12 weeks.

Dosing Regimen	Observed ALT >5X ULN[1]	Simulated ALT >5X ULN
Efavirenz 600 mg QD oral	1% to 8%	1% to 2%

Table 1. Comparison of observed vs. simulated hepatotoxicity for efavirenz

Conclusions

DILIsym correctly predicted infrequent hepatotoxicity for efavirenz, consistent with the low rate of ALT elevations seen clinically. This study demonstrates the ability of DILIsym to combine *in vitro* mechanistic data, predicted liver compound exposure, and biological variability to predict the incidence of liver injury. Thus, DILIsym represents a powerful tool to assess the potential DILI liabilities of new compounds. In addition, the efavirenz representation developed in the current study can be used to predict DILI drug-drug interactions between efavirenz and co-administered drug(s).

References

[1] Efavirenz. URL: https://livertox.nlm.nih.gov/Efavirenz.htm.

[2] Inger Darling. Efavirenz physiologically based pharmacokinetic model development and validation as a moderate cyp3a4 inducer for drug-drug interaction predictions. URL: https://www.simulations-plus.com/assets/M1430-13-87_aaps_efavirenz_poster_2019-10-18.pdf.

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