Quantitative Systems Toxicology Modeling Using DILIsym Suggests That Mitochondrial Biogenesis Could Explain Adaptation to Drug-Induced Liver Injury (DILI)

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INTRODUCTION

- Resolution of elevations of the liver injury biomarker serum ALT despite continued drug dosing, termed "adaptation", is commonly observed in clinical trials, but the underlying mechanisms behind this phenomenon remain unclear.
- Mitochondrial dysfunction is one of the major mechanisms underlying DILI. [1] When mitochondrial function is insufficient for energy demand, mitochondrial biogenesis is often activated and contributes to adaptation. [2-4]
- Solithromycin, a 4th generation macrolide developed for the treatment of community acquired pneumonia, caused serum ALT elevations in a minority of patients in clinical studies, with improvement often observed during continued dosing (or with rapid recovery thereafter). [5]
- DILIsym® is a quantitative systems toxicology (QST) model which integrates *in vitro* mechanistic toxicity data, *in vivo* dynamic drug disposition, known biochemistry, and patient characteristics. DILIsym predicts the hepatotoxic potential of new drug candidates and also provides an enhanced understanding of the mechanisms underlying compounds that generate liver signals in the clinic. [6]
- QST modeling of macrolide antibiotics using DILIsym showed that mechanisms underlying ALT elevations were significantly different within the same class of antibiotics. ALT elevations mediated by solithromycin and clarithromycin were predominantly due to mitochondrial electron transport chain (ETC) inhibition, whereas erythromycin effects were mainly due to bile acid (BA) transporter inhibition. [7]
- Mechanism analyses using QST modeling suggest that mitochondrial biogenesis might have contributed to the observed adaptation of solithromycin. In the current study, mitochondrial biogenesis was mechanistically represented within DILIsym, and its impact on time dependent ALT elevations resulting from solithromycin and other drugs was assessed.

METHODS

- The mitochondria sub-model within DILIsym [8] was updated to represent mitochondrial biogenesis. Relevant parameters were obtained from literature or optimized to ALT profiles in patients treated with solithromycin. [9,10]
- A simulated population (SimPops) that includes variability in hepatotoxicity mechanisms and mitochondrial biogenesis (Biogenesis SimPops) was created by imposing variability in biogenesis parameters on the existing human normal healthy volunteer SimPops (Standard SimPops)
- Seven exemplar drugs with different hepatotoxicity mechanisms were simulated in the standard and the biogenesis SimPops.

Compound	Simulated Dose	Major DILI Mechanism
Solithromycin	IV 400 mg (D1-3) + PO 800 mg QD (D4) + PO 400 mg QD (D5-7)	ETCi
Clarithromycin	PO 500 mg BID 1 week	ETCi
Tolcapone	PO 2000 mg TID 2 week	UC
Buprenorphine	PO 150 mg QD 2 week	ETCi, UC
AMG 009	PO 100 mg BID 2 weeks	BAi
Erythromycin	PO 500 mg QID 10 days	BAi
Acetaminophen	PO 20 g single dose	OS

ETCi: mitochondrial electron transport chain inhibition, UC: mitochondrial uncoupling, BAi: bile acid transporter inhibition , OS: oxidative stress.

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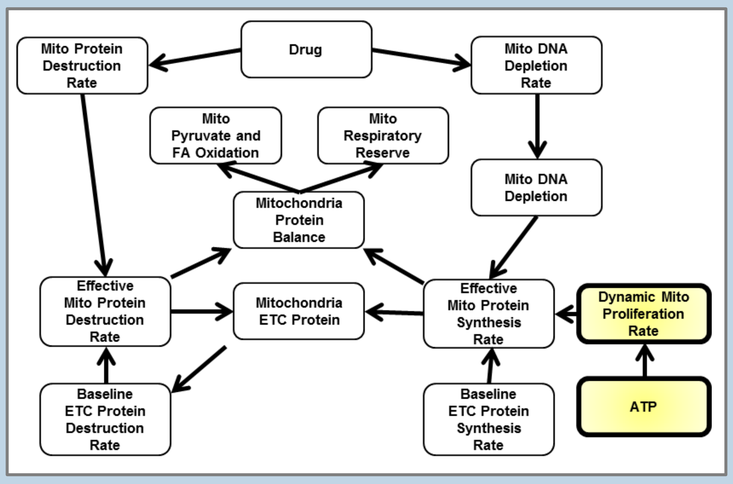
RESULTS

Mechanistic Modeling of Mitochondrial Biogenesis

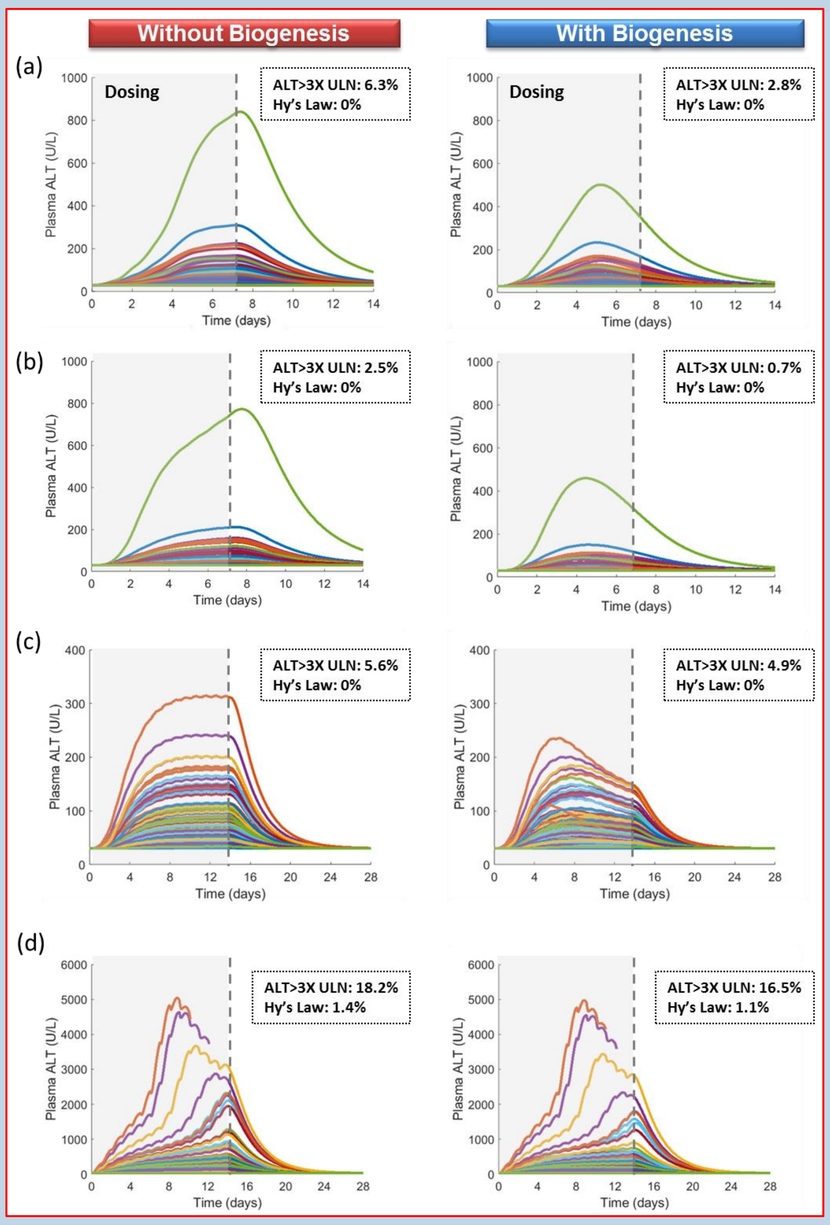


DILIsym Parameter	Unit	Value
Basal mitochondria ETC protein content[a]	mmol	$9.56e^{-14}$
Rate constant for baseline mitochondria ETC protein synthesis[a]	1/hr	0.0069
Mitochondria protein proliferation V_{max}[b]	mmol/hour	$1e^{-14}$
Mitochondria protein proliferation K_m[b]	dimensionless	0.8
Mitochondria protein proliferation Hill[b]	dimensionless	1.5
ATP decrement delay constant for mitochondria[b]	hr	96

[a] calculated using experimental data [9,10]
[b] optimized to ALT profiles in patients administered solithromycin

- Mitochondrial electron transport chain (ETC) protein content is determined by the balance of synthesis and destruction rates
- At steady-state, baseline synthesis and destruction rates are equal
- Changes in mitochondrial protein balance subsequently affects mitochondrial ETC function, pyruvate and fatty acid oxidation, and the respiratory reserve
- The effective synthesis rate is regulated by changes in liver ATP and mtDNA content
- Biogenesis SimPops represent variability in the Mitochondrial protein proliferation Vmax with S.D. of ±30% and the parameter range of 2.5 times the S.D (validated with solithromycin clinical data).

Simulated Liver Enzyme Profiles in the Absence and Presence of Mitochondrial Biogenesis



(a) Solithromycin

- ALT elevations in excess of those observed clinically were predicted in a subset of individuals which was normalized after discontinuation of treatment.
- With biogenesis, ALT peaks occur earlier and resolve with continuing treatment, consistent with the clinical data.

(b) Clarithromycin

- Similar pattern of adaptation as shown in the solithromycin case predicted with mitochondrial biogenesis.

(c) Tolcapone

- With biogenesis, the frequency of DILI decreased, and ALT resolved with continuing treatment

(d) Buprenorphine

- Biogenesis slightly decreased the DILI frequency, but Hy's Law cases were predicted in 1.1% of simulated individuals even with biogenesis, suggesting that biogenesis effects can be overcome by severe mitochondrial injury

Mitochondrial biogenesis did not alleviate hepatotoxicity mediated by bile acid transporter inhibition (**erythromycin, AMG 009**) or oxidative stress (**acetaminophen**).

Simulated plasma ALT profiles in the human SimPops (n=285) treated with (a) solithromycin, (b) clarithromycin, (c) tolcapone, or (d) buprenorphine in the absence (left) and presence (right) of mitochondrial biogenesis. Liver enzyme elevations were predicted in a simulated human population (n=285) administered exemplar compounds by combining PBPK-predicted exposure and mechanistic toxicity data. Each line represent a simulated individual.

CONCLUSIONS

- QST modeling suggests that mitochondrial biogenesis can mitigate DILI caused by mitochondrial dysfunction.
- Mitochondrial biogenesis may be one of the mechanisms underlying DILI adaptation.
- More *in vitro* and clinical data are needed to better quantitate the timing, extent, and inter-individual variability of biogenesis and to enhance the accuracy of prospective predictions of adaptation to DILI.

DILI-sim Initiative

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