Quantitative Systems Toxicology Modeling Using DILIsym Suggests That Drug-Induced Liver Injury (DILI) Can Be Enhanced by Co-administered Drugs and Mitigated by Mitochondrial Biogenesis

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PURPOSE

Drug-induced liver injury (DILI) can be enhanced by polypharmacy if co-administered drugs induce toxicity via mechanisms that have overlapping pathways. Resolution of DILI despite continued drug dosing, termed “adaptation”, is commonly observed in clinical trials, but the underlying mechanisms behind this phenomenon remain unclear. In the phase 3 clinical trials of solithromycin, DILI with partial adaptation was observed in two patients concomitantly treated with metformin. [1] Solithromycin interferes with mitochondrial respiration and this appears to be the major mechanism underlying its potential to cause liver injury. In the current study, the potential interaction between metformin and solithromycin and mechanisms underlying DILI adaptation were investigated using DILIsym®, a quantitative systems toxicology (QST) modeling platform.

METHODS

A solithromycin model was previously constructed within DILIsym. [2] A physiologically-based pharmacokinetic (PBPK) model of metformin was constructed within DILIsym to describe the disposition of metformin. To assess the potential mitochondrial and oxidative stress liabilities of metformin, *in vitro* cellular assays were performed in HepG2 cells using a Seahorse XFe96 Flux Analyzer and a high content imaging technique, respectively. To evaluate the clinical risk of DILI, simulations were performed by combining hepatic exposure predicted by PBPK models and mechanistic hepatotoxicity parameters derived from in vitro assays. A simulated population (SimPops™) that includes variability in hepatotoxicity mechanisms and mitochondrial biogenesis was employed in simulations to assess the population variability. Simulated dosing protocols are as below:

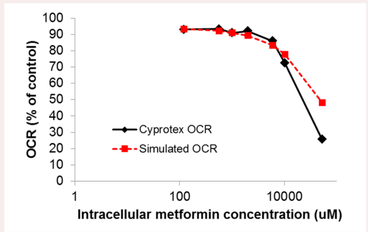
- Metformin 1 g BID for 4 weeks
- Solithromycin IV 400 mg on days 1-3, PO 800 mg on day 4, PO 400 mg on days 5-7 (IV-to-Oral protocol)
- Metformin 1 g BID for 4 weeks + Solithromycin IV-to-Oral protocol during the 4th week

Simulations were performed in the absence and presence of mitochondrial biogenesis to evaluate the potential impact of mitochondrial biogenesis on simulated hepatotoxicity.

REFERENCES

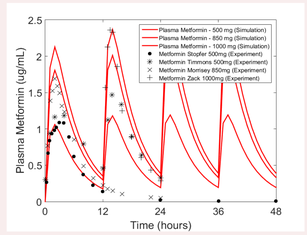
[1] FDA briefing document. Solithromycin oral capsule and injection meeting of antimicrobial drugs advisory committee.
[2] Woodhead et al., 2019. Pharm Res. 36, 48.
[3] File et al., 2016. Clin Infect Dis Off Publ Infect Dis Doc Am. 63, 1007-1016.

RESULTS



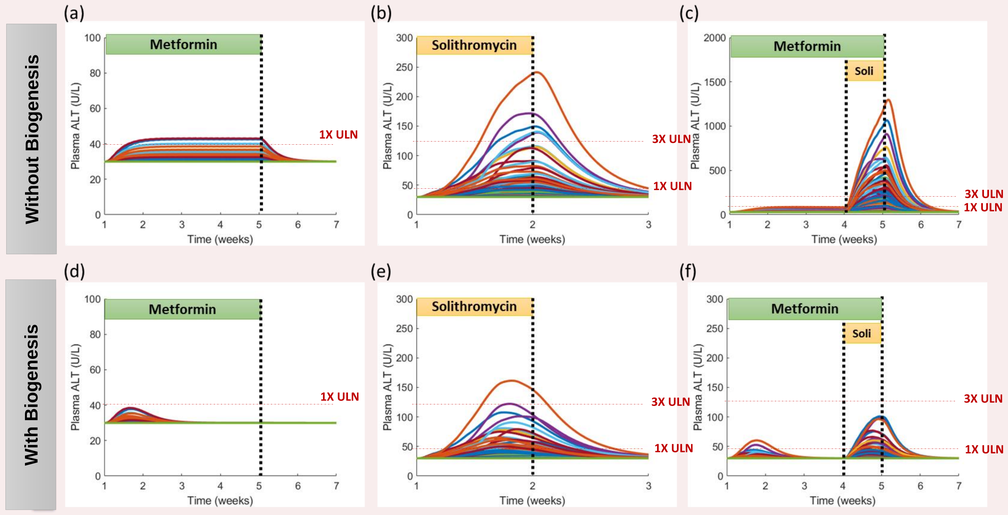
Metformin *in vitro* toxicity data

- The *in vitro* assay results in HepG2 cells indicated that metformin is a mitochondrial electron transport chain (ETC) inhibitor
- DILIsym parameters for metformin-mediated ETC inhibition derived from *in vitro* data



Metformin PBPK modeling

- Simulated plasma metformin concentration-time profiles generally recapitulate clinical PK data



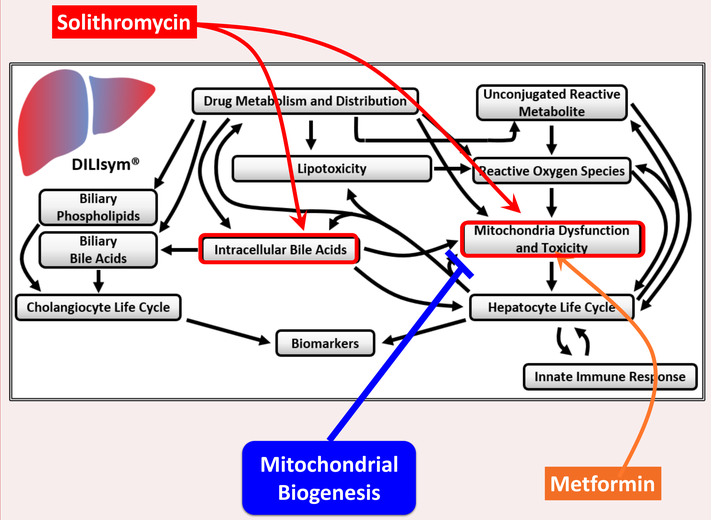
Simulated plasma ALT profiles in the human SimPops (n=285)

- Simulations of metformin alone predicted very mild ALT elevations (< 1.5X ULN) in a subset of individuals, consistent with known liver safety of metformin; simulated ALT elevations resolved within 2.5 weeks even with continuing treatment in the presence of mitochondrial biogenesis (a,d)
- Simulations of solithromycin alone predicted modest ALT elevations > 3X ULN in a subset of individuals; in the presence of mitochondrial biogenesis, simulated ALT peaked on day 4 and resolved with continuing treatment, consistent with clinically observed ALT dynamics (b,e) [3]
- When solithromycin was given to subjects who had been taking metformin, simulations without mitochondrial biogenesis predicted enhanced ALT elevations, suggesting a potential DILI DDI between metformin and solithromycin which have overlapping hepatotoxicity mechanisms (i.e., mitochondrial dysfunction) (c)
- Simulated DILI DDI was mitigated by mitochondrial biogenesis, which had been activated by the pretreatment of metformin by the time solithromycin was administered (f)

CONCLUSIONS

- QST modeling suggests that co-administered drugs can potentiate DILI due to interactions of toxicological effects, and adaptation to DILI may, in part, be attributed to mitochondrial biogenesis.
- More experimental data are needed to better quantitate the extent and inter-individual variability of biogenesis and to enhance the accuracy of prospective predictions of adaptation to DILI.

Mechanisms of DILI and Adaptation



DISCLOSURES

Kyunghee Yang, Christina Battista, Jeffrey Woodhead, Brett Howell, and Scott Siler are employees of DILIsym Services Inc.

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