Assessment of the Mechanism for Remdesivir-Associated Clinical ALT Elevations Using DILIsym Quantitative Systems Toxicology Modeling

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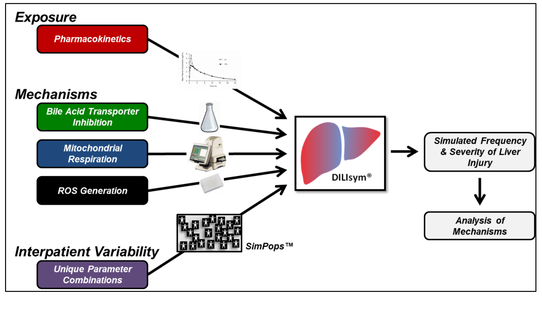
Introduction

- Remdesivir, a monophosphoramidate prodrug of a nucleoside analog, has been granted Emergency Use Authorization in the U.S. for the treatment of hospitalized COVID-19 patients.
- In a Ph1 clinical study in healthy volunteers treated with the 150 mg daily dose of remdesivir for 7 or 14 days (higher than the current clinical dose) [1], reversible low- grade elevations of serum ALT and AST were observed at 5-25 days after the first dose in 8 out of 16 individuals.

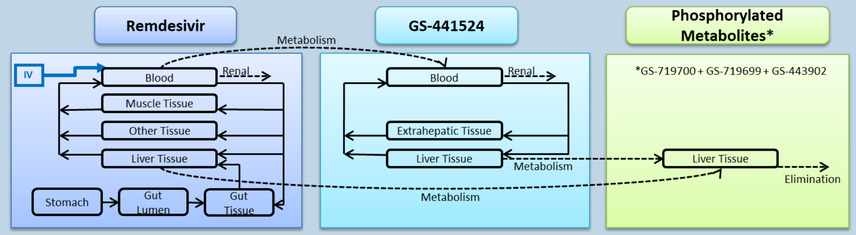
Methods

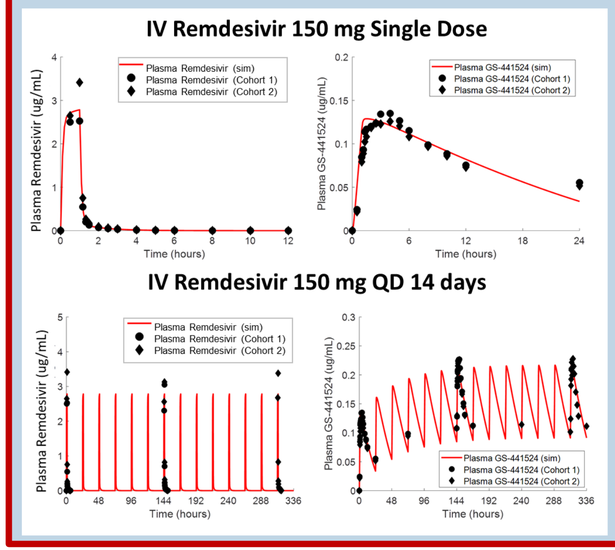
The underlying potential mechanisms of observed liver signals were investigated leveraging DILIsym®, a quantitative systems toxicology (QST) modeling platform. DILIsym integrates:

- Clinical drug exposure predicted by a physiologically-based pharmacokinetic (PBPK) model
- *In vitro* data to assess the potential for remdesivir to induce oxidative stress, mitochondrial dysfunction, and inhibition of bile acid transporters
- Inter-individual variability in hepatotoxicity pathways (SimPops)



Parameterization of Clinical PK Data





The PBPK representation for remdesivir and its metabolites was constructed with clinical data from Phase I trial results. Simulated AUC and C_{max} values were within 25% of clinical data.

Conclusions

- **Clinically-observed reversible low-grade ALT increases following multiple dose treatment with 150 mg of remdesivir for 7 or 14 days are unlikely to be due to mitochondrial electron transport chain or bile acid transport inhibition, indicating potentially alternative mechanisms.**

Acknowledgements

- The members of the DILI-sim Initiative

Reference: [1] Humeniuk (2020) Clin Transl Sci. 13(5):896-906.

Parameterization of *in vitro* Toxicity Data

Compound	Mechanism	Parameter	Unit	Value*
Remdesivir	Bile Acid Transport Inhibition	Inhibition constant (IC_{50}) for BSEP	µM	22
		Inhibition constant(IC_{50}) for basolateral efflux	µM	5.1
		Inhibition constant(IC_{50}) for NTCP	µM	72
Phosphorylated metabolites†	Mitochondrial Dysfunction	Coefficient for ETC Inhibition 1	µM	4203

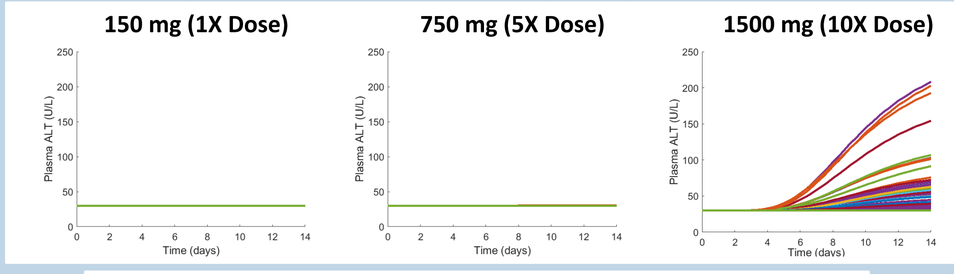
DILIsym parameter values identified from *in vitro* mechanistic toxicity data.

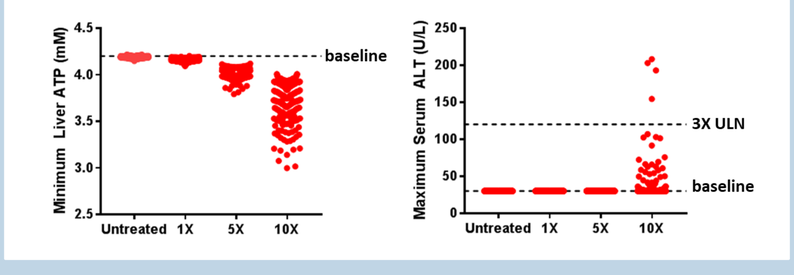
* Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value.

† Mono-, di-, and tri-phosphorylated metabolites (GS-719700 + GS-719699 + GS-443902).

Simulation Results

Simulated Hepatic Biomarkers in SimPops (n=300) administered remdesivir





- DILIsym predicted no systemic ALT elevations or liver ATP reductions for the remdesivir multiple dose treatment (1-hr IV infusion of 150 mg QD for 2 weeks) in SimPops.
- Dose escalation simulations showed that a dose 10-fold above the current clinical dose was required to elicit ALT elevations and liver ATP reductions.

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