Providing Insight into Novel Dosing Protocols Using a Quantitative Systems Pharmacology (QSP) Model of Drug-Induced Liver Injury

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ABSTRACT

Objective: Elevations in serum alanine aminotransferase (ALT) were observed in phase I clinical studies for a novel investigational anti-infective therapy (Compound X). Previously conducted in vitro and cellular assays identified oxidative stress and mitochondrial electron transport chain (ETC) inhibition as potential mechanisms for the ALT elevations. A novel dosing protocol for Compound X had been proposed; this work would use quantitative systems pharmacology (QSP) modeling to predict the safety of this protocol.

Methods: A model for Compound X was created within DILysm®, a QSP platform for predicting drug-induced liver injury (DILI). DILysm® was then used to predict the potential safety margin for the novel Compound X dosing protocol.

Results: DILysm® recapitulated the clinical dose response with reasonable accuracy after optimization. While the novel protocol had a narrow safety margin, DILysm® results suggested that severe liver injury could be prevented if patients were monitored for ALT elevations daily and dosing halted when ALT was found to be above 3-fold higher than the upper limit of normal. Furthermore, the predicted safety margin of the drug improved when dosing was given on a weight-adjusted basis for each patient.

Conclusions: Modeling using DILysm® suggested modifications to the dosing protocol that could potentially make the drug safer. These results suggest the utility of QSP methods in optimizing drug dosing protocols for maximum safety.

INTRODUCTION

- Compound X is a novel pharmaceutical developed for the treatment of an important short-term condition. It is designed to be dosed intravenously (IV) in an inpatient setting.
- Liver signals were observed in the clinic when 4x the proposed clinical dose was given daily as a 22-hour infusion and when a 2x dose was given thrice-daily as a 1-hour infusion.
- The company developing Compound X wished to explore a 4-hour IV infusion protocol using a 0.75x dose.
- DILysm® was employed to explore the difference in toxicity among the existing protocols and to estimate the potential safety margin for the novel dosing protocol.

METHODS

- A PBPK model of Compound X was constructed using the PBPK sub-model in DILysm® in order to predict potential liver exposure of the compound. Maximum and minimum exposure was represented by modulating the simulating dose.
- In vitro data on bile acid transporter inhibition, mitochondrial toxicity, and oxidative stress was generated. Compound X was shown to generate oxidative stress and to inhibit the mitochondrial electron transport chain (ETC). Compound X also mildly inhibited glycolysis.
- Toxicity parameter inputs calculated from the in vitro data were used to make initial predictions on toxicity in DILysm®. Simulations in DILysm® SimPops™ Human_ROS_apop_mito_v18_B were performed for each dosing regimen.
- Toxicity parameters were then adjusted so that the clinically observed dose response was recapitulated by DILysm® while preserving the effect of the mechanisms flagged by the in vitro assays.
- Prospective predictions were made using these adjusted toxicity parameters for the proposed dose, escalating upwards until simulated toxicity was observed.
- The simulations were performed with and without strict ALT monitoring criteria and with weight-adjusted dosing in order to understand whether these protocol modifications improved the safety profile of Compound X.

CONCLUSION

- The margin of safety for the proposed 0.75x 4-hour infusion protocol was predicted to be small.
- Employment of a stringent stop protocol, where ALT is measured daily and dosing is stopped if an ALT elevation above 3X greater than the upper limit of normal (ULN) is observed, would increase the safety margin for severe liver injury.
- The safety profile of Compound X can be improved to 4.5x by dosing on a weight-adjusted basis.
- QSP modeling can be used to explore the toxicity risk of novel dosing protocols, allowing for the more informed selection of future clinical trials.

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