Mechanistic Modeling with DILIsym® Predicts Species Differences in CKA via Multiple Hepatotoxicity Mechanisms

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Objectives: To predict species differences in CKA-mediated hepatotoxicity using DILIsym®, a mechanistic model of drug-induced liver injury (DILI)

Methods: Inhibitory effects of CKA on bile acid (BA) and bilirubin transporters were assessed using transporter-overexpressing vesicles and cells. CKA-mediated oxidative stress and mitochondrial dysfunction were determined in HepG2 cells. These in vitro data were used to define hepatotoxicity parameters and combined with PBPK sub-model simulations of hepatic compound exposure to predict DILI in DILIsym®. Previously constructed human and rat simulated populations (SimPops™) that incorporate variability in the aforementioned toxicity mechanisms were utilized to determine the impact of inter-individual variability upon administration of single CKA doses of 900mg and 500mg/kg, respectively.

Results: CKA induces oxidative stress (oxidative stress production rate constant=7278mL/mol/hr human, 9705mL/mol/hr rat) and inhibits mitochondrial electron transport chain (ETC) flux (ETC inhibition coefficient=14.2mM human, 1.42mM rat). CKA inhibits human BSEP (IC₅₀=129.7µM), rat Bsep (IC₅₀=94µM), human MRP3 (IC₅₀=11.2µM), human NTCP (IC₅₀=19.5µM), rat Mrp2 (IC₅₀=68.5µM), and human OATP (IC₅₀=0.84µM) [1]. CKA was modeled as a noncompetitive inhibitor of BSEP/Bsep and MRP3/Mrp3 and a competitive inhibitor of NTCP/Ntcp. Due to lack of data, IC₅₀ values for NTCP/Ntcp, MRP3/Mrp3, MRP2/Mrp2, and OATP/Oatp were assumed the same across species. Human SimPops™ predicted modest increases <1.5x upper limit of normal (ULN) in serum ALT, recapitulating the clinical data. Rat SimPops™ predicted ALT elevations >3xULN in 36.4% of the population, slightly underpredicting the 75% observed in preclinical trials (Figure 1). DILIsym® recapitulated preclinical observations in bilirubin increase due to both DILI and bilirubin transporter inhibition. Rat SimPops™ predicted increases in total bilirubin >2xULN for 100% of the population, mirroring preclinical data. Conversely, no significant increases in bilirubin were observed in human SimPops™, consistent with clinical observations.

Conclusions: Using in vitro data to determine toxicity parameters, DILIsym® accurately predicted CKA hepatotoxicity in rats and not in humans, consistent with observed preclinical and clinical data.

References