USE OF QUANTITATIVE SYSTEMS TOXICOLOGY (QST) TO IDENTIFY POTENTIAL INTRINSIC MECHANISMS OF TOXICITY

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PURPOSE

BAY1128688, a selective inhibitor of aldo-keto reductase family 1 member C3 (AKR1C3), was in clinical trials as a potential therapy to provide pain relief for women with endometriosis. Although no liver toxicity was observed in rats and cynomolgus monkeys after 13 weeks of treatment and in humans after 4 weeks of treatment, clinical development was prematurely terminated due to post-treatment hepatotoxicity[1] following administration of 30mg QD or 60mg BID for 12 weeks. This finding prompted use of DILIsym®, a QST model, to determine possible mechanisms contributing to the observed drug-induced liver injury (DILI)[2,3]. Although bilirubin elevations >2x upper limit of normal (ULN) and alanine aminotransferase (ALT) elevations >2xULN were observed in some individuals while on treatment, severe ALT elevations >3xULN were mostly observed at the end-of-treatment visit (12 weeks after starting treatment) or after treatment cessation. The timing for hepatotoxicity presents an opportunity to explore mechanisms that may increase risk for delayed hepatotoxicity in susceptible individuals using DILIsym.

OBJECTIVE

To investigate whether a QST model could account for liver chemistry abnormalities observed during BAY1128688 treatment and provide insight into mechanisms driving hepatotoxicity and bilirubin elevations.

METHODS

Mechanistic in vitro data and a physiologically based pharmacokinetic (PBPK) model developed with clinical exposure data were utilized to predict the hepatotoxic liability of BAY1128688 in a simulated population (SimPops™) that represents inter-patient variability. A sensitivity analysis was performed to determine which intrinsic mechanism of toxicity included in DILIsym – oxidative stress, mitochondrial toxicity, or bile acid transporter inhibition – was the largest contributor to predicted ALT elevations. Initial simulations used a quantitative structural activity relationship (QSAR) predicted liver partition coefficient, and the default mode of bile acid transporter inhibition (mixed inhibition type with α=5) was applied. Following initial simulations and mechanistic sensitivity analysis, the parameterization around mode of bile acid transporter inhibition and liver partition coefficient were explored and refined to bring simulations into better alignment with the bilirubin and ALT elevations observed in patients. After optimization with the data from the highest clinical dose group, 60mg BID for 12 weeks, all lower clinical doses were simulated and compared to clinical observations for ALT and bilirubin.

RESULT

A PBPK model for BAY1128688 was successfully optimized and validated using clinical data following single or repeat daily (QD) dosing. Based on PBPK model predictions for exposure and the potential effects of BAY1128688 on intrinsic toxicity mechanisms included in DILIsym, initial simulations indicated hepatotoxic liabilities but overpredicted the incidence of ALT and bilirubin elevations. Sensitivity analyses indicated that the inhibitory effect of BAY1128688 on bile acid transport was the dominant toxicity mechanism leading to simulated ALT elevations, and BSEP inhibition was shown to be the most impactful for ALT elevations. As a result of the liver partition coefficient optimization, simulations of BAY1128688-induced alterations in bilirubin disposition matched on treatment clinical data with peak bilirubin 4-6 mg/dL following 60 mg BID. In addition, the mode and potency of BSEP and basolateral inhibition were adapted, and simulation results captured the peak ALT ~100 U/L, similar to on treatment clinical observations in the 60 mg BID cohort. Simulations showed DILIsym reproduced dose-dependent changes in frequency of bilirubin elevations, although the magnitude sometimes observed at lower doses was not captured. DILIsym reproduced on treatment ALT elevations at 60 mg BID but did not capture elevations at lower doses as well as elevations after end of treatment.

CONCLUSION

While DILIsym is not currently capable of directly predicting post-treatment ALT elevations as were observed with BAY1128688, simulations indicated dose-dependent intrinsic toxicity that is believed to be a necessary initial step in what was likely an adaptive immune response[4]. The approach taken herein can be used to inform predictions of drug-mediated intrinsic hepatotoxicity not evident in current preclinical testing, and that may be a prerequisite for delayed toxicity mediated by adaptive immune mechanisms.

REFERENCES

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4. Mosedale. Clin Pharmacol Ther 2017; 101(4):469.

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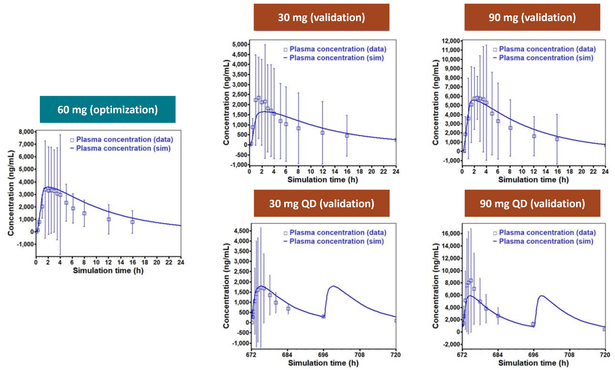
QST modeling provides insights into mechanisms driving hepatotoxicity

PBPK MODEL FOR BAY1128688 REPRODUCES OBSERVED CLINICAL EXPOSURE

PBPK model for BAY1128688 developed in GastroPlus®

- Clinical data following single dose of 60 mg BAY1128688 used for model optimization
- PBPK model subsequently validated with clinical data not used during optimization, i.e., 30 or 90 mg single dose and 30 or 90 mg QD for 1 month

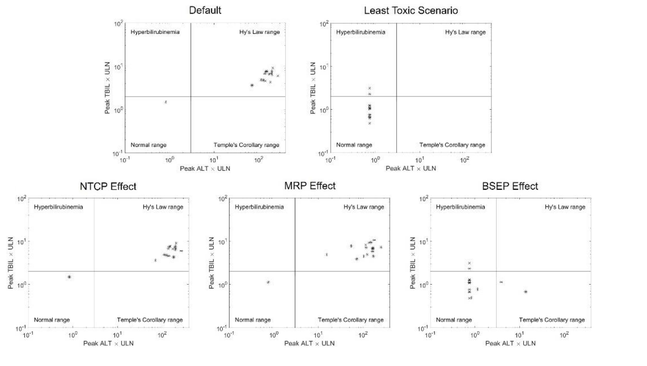


Simulated (blue line) and observed (blue squares) plasma concentrations of BAY1128688 following single and multiple doses. Simulation results are shown for an average individual. Subsequent simulations were conducted to represent PK variability across a population of simulated individuals (N= 285).

SIMULATIONS USED TO IDENTIFY MAIN MECHANISM DRIVING HEPATOTOXICITY

Effect of BAY1128688 on bile acid transporter inhibition drives liver injury

- BAY1128688 predicted to induce hepatocyte death due to bile acid accumulation (i.e., inhibition of bile acid transporters)
- Exploration of bile acid transporter, i.e., BSEP, MRP, NTCP, inhibition indicates BSEP inhibition has strongest impact on ALT elevations

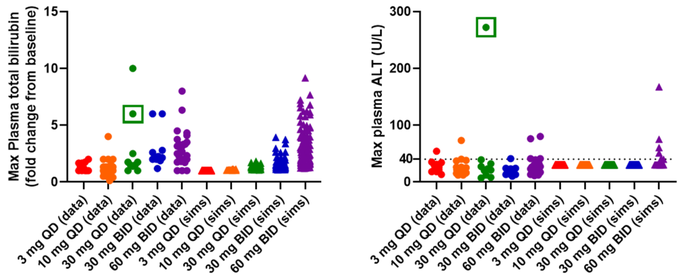


Evaluation of drug-induced serious hepatotoxicity (eDISH) plots of the effect of different types of bile acid inhibition on transporter s that are inhibited by BAY1128688 in a smaller, sensitive set of simulated patients (SimCohorts). The mode of inhibition for the indicated bile acid transporter was altered to reduce bile acid accumulation in hepatocytes. Fold change in peak ALT is shown along the x-axis (vertical line is 3xULN) and fold change in peak total bilirubin is shown along the y-axis (horizontal line is 2xULN).

SIMULATION RESULTS CONSISTENT WITH CLINICAL OBSERVATIONS

Simulated results reproduce dose-dependent biomarker elevations

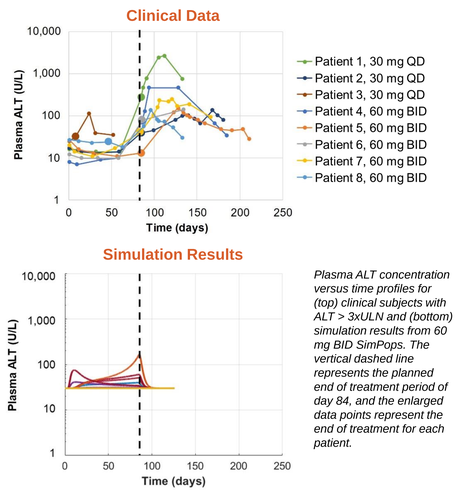
- On treatment bilirubin elevations, in the absence of ALT elevations at that point in time, suggest altered bilirubin disposition rather than liver injury
- Clinically observed bilirubin elevations while on treatment were used to optimize liver partition coefficient and bring simulated bilirubin elevations in line with clinical data based on 60 mg BID exposure and potential BAY1128688 effects on bilirubin disposition as, indicated by *in vitro* studies
- The mode and potency of BSEP and basolateral inhibition were adapted to bring simulations into alignment with magnitude and delayed timing for clinical ALT elevations



Clinical measurements (circles) and simulated values (triangles) for maximum plasma total bilirubin fold change from an individual's baseline and maximum plasma ALT. Patient #1, as indicated by the green box, experienced the highest ALT elevation with 30 mg QD treatment. The horizontal dotted line indicates the ULN for ALT in DILIsym.

Simulated timing of on-treatment ALT elevations aligns with clinical data

- Clinical data indicate most ALT elevations were observed at the end-of-treatment visit (12 weeks after starting treatment) or after treatment cessation
- Simulation results reproduce modest on-treatment ALT elevations in the 60 mg BID protocol
- Timing for ALT elevations consistent with clinical observations while on treatment
- Drug exposure and intrinsic mechanisms of toxicity appear sufficient to perturb liver homeostasis and increase risk for delayed liver injury



Plasma ALT concentration versus time profiles for (top) clinical subjects with ALT > 3xULN and (bottom) simulation results from 60 mg BID SimPops. The vertical dashed line represents the planned end of treatment period of day 84, and the enlarged data points represent the end of treatment for each patient.

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