M-25

MECHANISTIC MODELING WITH DILISYM® PREDICTS DOSE-DEPENDENT CLINICAL HEPATOTOXICITY OF AMG 009 THAT INVOLVES BILE ACID TRANSPORTER INHIBITION

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Abstract

Objectives: To predict the clinical hepatotoxicity of AMG 009 and species differences in AMG 009-mediated hepatotoxicity using DILIsym®, a mechanistic model of drug-induced liver injury

Methods: Inhibitory effects of AMG 009 for bile acid transporters were assessed using transporter-overexpressing vesicles and transfected cells. Hepatotoxicity responses to AMG 009 in humans and rats were simulated in DILIsym® using a PBPK model of AMG 009, bile acid homeostasis and toxicity sub-models,[1,2] and *in vitro* bile acid transporter inhibition data. Previously constructed human and rat simulated populations (SimPops™) that incorporate variability in bile acid disposition and mitochondrial function were employed for population analyses.

Results: AMG 009 was a mixed inhibitor of human BSEP (K_i=2.4 μM; α=2.4), rat Bsep (K_i=5.6 μM; α=34), and human MRP4 (K_i=12.9 μM; α=2.1), and a weak inhibitor of human NTCP (IC_{50}=126.5 μM) and rat Ntcp (IC_{50}=48.4 μM). Employing only AMG 009-specific data, modeling of 100 mg AMG 009 bid for 14 days predicted serum ALT elevations >3X upper limit of normal (ULN) in 17% of the human SimPops™; this was similar to the clinically observed incidence of 12.5% (1 out of 8). DILIsym® recapitulated the clinically observed ALT dynamics (e.g., delayed hepatotoxicity presentation, recovery after discontinuation). Predicted incidence of Hy's Law cases (ALT>3X ULN and bilirubin>2X ULN) was 1.4%, whereas no Hy's Law cases were observed among 8 individuals administered 100 mg. At 25 and 50 mg dosing, minimal toxicity was predicted (0 and 2% of ALT>3X ULN, respectively; no Hy's Law cases), consistent with the clinical data. Conversely, no hepatotoxicity was predicted in the rat SimPops™ administered 1500 mg/kg/day AMG 009 for 1 month, consistent with the preclinical data.

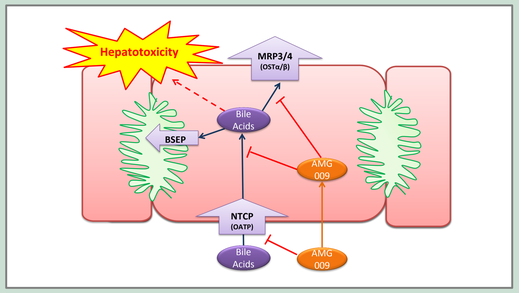
Conclusions: DILIsym® predicted dose-dependent, delayed AMG 009 hepatotoxicity in humans but no hepatotoxicity in rats, consistent with observed clinical and preclinical data. Mechanistic modeling is a useful approach to translate *in vitro* bile acid transporter inhibition data to clinical hepatotoxicity.

Introduction

- Clinical development of AMG 009 was discontinued because of dose-dependent hepatotoxicity observed in phase I multiple dose studies; hepatotoxicity resolved upon cessation of treatment. Hepatotoxicity was not observed in preclinical animals.[3]
- AMG 009 showed no liability for reactive metabolite formation and mitochondrial toxicity; bile acid transport inhibition was the only effect distinguishing AMG 009 from safe drugs.
- DILIsym® is a systems pharmacology model of DILI that incorporates drug/metabolite disposition, bile acid physiology and pathophysiology, the hepatocyte life cycle, and liver injury biomarkers.

Results

Mechanism of AMG 009 Hepatotoxicity



In Vitro Transporter Assays

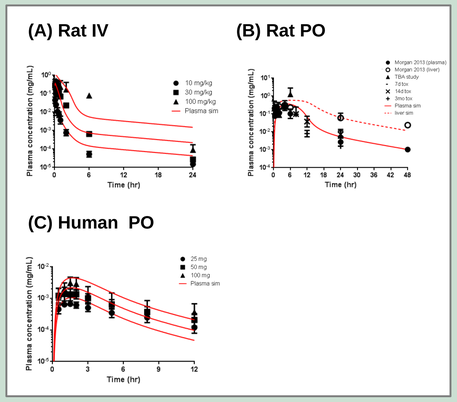
Transporter	K_i (μM)	Type
Human BSEP	2.4	Mixed (α = 2.4)
Rat Bsep	5.6	Mixed (α = 34)
Human MRP4	12.9	Mixed (α = 2.1)
Human NTCP	126.5*	-
Rat Ntcp	48.4*	-

*IC_{50} values

AMG 009 is a potent inhibitor of hepatic bile acid transporters, which might lead to hepatic bile acid accumulation and subsequent toxicity.

BSEP, bile salt export pump; NTCP, sodium-taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; MRP, multidrug resistance-associated protein; OST, organic solute transporter.

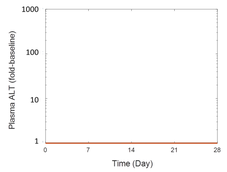
PBPK Simulations



PBPK models reasonably predicted plasma and liver concentrations of AMG 009 in rats and humans.

Closed and open symbols represent observed plasma and liver concentrations of AMG 009, respectively. Solid and dashed lines represent simulated plasma and liver concentrations of AMG 009, respectively.

Rat Hepatotoxicity Simulations

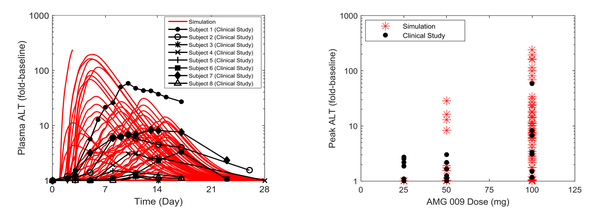


	DILIsym® Simulation
	1500 mg/kg
ALT > 3X ULN	0/187 (0%)
Bili > 2X ULN	0/187 (0%)

DILIsym® predicts no hepatotoxicity in rat SimPops™, consistent with the preclinical data.

Simulated ALT profiles and summary of simulated serum biomarkers in simulated rat populations (SimPops™) administered 1500 mg/kg AMG 009 orally for 1 month.

Human Hepatotoxicity Simulations



	Clinical Trial	DILIsym® Simulation		
	100 mg	25 mg	50 mg	100 mg
ALT > ULN	5/8 (62.5%)	0/212 (0%)	7/212 (3.3%)	45/212 (21.2%)
ALT > 3X ULN	1/8 (12.5%)	0/212 (0%)	4/212 (1.9%)	36/212 (17.0%)
ALT > 10X ULN	1/8 (12.5%)	0/212 (0%)	2/212 (0.9%)	18/212 (8.5%)
Bili > 2X ULN	0/8 (0%)	0/212 (0%)	0/212 (0%)	3/212 (1.4%)
Hy's Law	0/8 (0%)	0/212 (0%)	0/212 (0%)	3/212 (1.4%)

DILIsym® predicts dose dependence and time course of AMG 009 hepatotoxicity and recovery after discontinuation, consistent with the clinical data.

A) Simulated and observed serum ALT profiles in humans administered 100 mg AMG 009 bid for 14 days. B) Simulated and observed peak serum ALT levels in humans administered 25, 50, or 100 mg AMG 009 bid for 14 days. AMG 009-mediated hepatotoxicity in simulated human populations (SimPops™) and clinical trials are summarized in the Table.

Methods

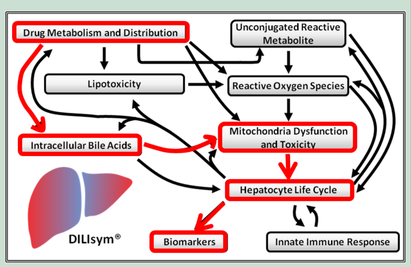
Assessment of inhibitory effects of AMG 009 for bile acid transporters Inhibitory effects of AMG 009 for bile acid transporters were assessed in isolated membrane vesicle transport systems (human BSEP, human MRP4, and rat Bsep) and cell lines overexpressing human NTCP or rat Ntcp. The kinetic parameters (K_m, V_{max}, and K_i) and type of inhibition were determined by fitting competitive, noncompetitive, uncompetitive, and mixed inhibition models to the untransformed data by nonlinear regression analysis. The best-fit model was assessed from visual inspection of the observed versus predicted data and Akaike Information Criterion.

Physiologically-based pharmacokinetic (PBPK) model development Human and rat PBPK models of AMG 009 were developed using in vitro and in vivo pharmacokinetic data available.

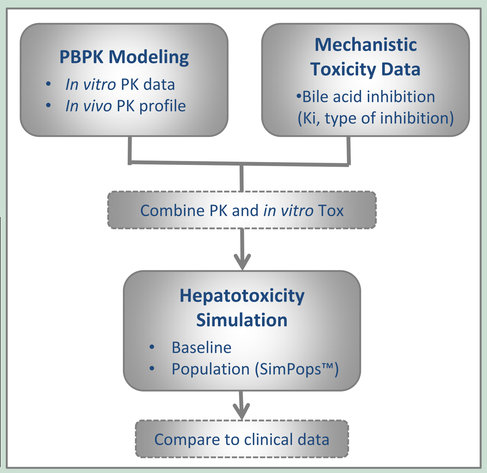
Construction of human virtual population (SimPops™) Human population samples (n=212) with variability in 15 parameters in the bile acid homeostasis, mitochondrial function, body weight, and hepatocyte regeneration was constructed previously within DILIsym® using the probability distribution of each parameter obtained from the literature. In rat population samples (n=187), parameters governing bile acid disposition were varied.

Simulation of DILI responses AMG 009-mediated perturbation of bile acid disposition and DILI responses were simulated in rat and human SimPops™ using PBPK model predictions of AMG 009 disposition, a previously developed bile acid homeostasis sub-model[1], and in vitro bile acid transport inhibition data.

DILIsym® Diagram



Modeling Approach



Conclusion

- Mechanistic modeling based on pharmacokinetic information and in vitro transporter inhibition data adequately predicted dose- and time-dependent hepatotoxicity of AMG 009 in humans.
- Use of species-specific bile acid model recapitulated species differences in hepatotoxicity of bile acid transporter inhibitors.
- Mechanistic models that integrate physiological information and experimental data can evaluate DILI mechanisms and may be useful to prospectively predict hepatotoxic potential of new drug candidates.

References

1. Woodhead JL et al. CPT:PSP 3:e123, 2012.
2. Woodhead JL et al. J Pharmacokinet Pharmacodyn 41:1(suppl) M-054, 2014.
3. Morgan et al. Tox Sci 136(1):216-241, 2013

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DILIsym®

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