Quantitative Systems Toxicology Modeling Supports Safety Determination for Ubrogepant, a Novel CGRP Inhibitor

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ABSTRACT

Objectives: CGRP inhibitors are a class of drugs that meet a significant unmet medical need for migraine treatments. However, two CGRP inhibitors, telcagepant and MK-3207, failed in clinical trials due to liver toxicity (1,2). Telcagepant, MK-3207, and the next-in-class compound ubrogepant were represented in DILIsym, a quantitative systems toxicology (QST) model of drug-induced liver injury, in order to predict whether ubrogepant would be a safer alternative.

Methods: *In vitro* experiments were undertaken determining the potential for the three compounds to inhibit bile acid transporters, cause mitochondrial dysfunction, and produce oxidative stress. The results of the *in vitro* assays were used to produce a representation of each compound in DILIsym, along with a PBPK model of each compound. The clinical doses of telcagepant and MK-3207 at which liver toxicity was observed were simulated, as well as a range of potential ubrogepant clinical protocols.

Results: Each of the molecules tested displayed signals in the *in vitro* assays for bile acid transporter inhibition, oxidative stress generation, and mitochondrial dysfunction. DILIsym correctly predicted the liver toxicity of telcagepant and MK-3207, while ubrogepant was predicted to be safe even at doses 10X the proposed clinical dose. Subsequent clinical trials demonstrated that ubrogepant was indeed safe (3), and the drug was approved by the FDA for the acute treatment of migraine.

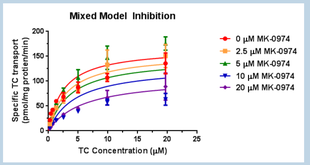
Conclusions: QST modeling can prospectively differentiate between toxic and non-toxic drugs within the same class and identify which drugs within a class carry less risk of toxicity. These applications can contribute to success in the clinic and regulatory approval of new drugs.

OVERVIEW

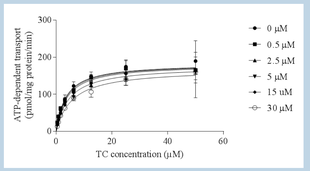
- CGRP inhibitors are a potentially valuable treatment for acute treatment of and prevention of migraines
- Two CGRP inhibitors, telcagepant and MK-3207, caused liver injury signals in clinical trials
- A novel CGRP inhibitor, ubrogepant, has been developed for acute treatment of migraine
- A comparison between ubrogepant and the two failed CGRP inhibitors would be useful for determining whether or not ubrogepant may have the same liver liabilities as the first-in-class drugs.
- The three compounds were simulated in DILIsym in order to:
  - Represent the known clinical toxicity of telcagepant and MK-3207, and
  - Predict the potential safety of ubrogepant prospectively.
- *In vitro* experiments were performed with each three compounds in order to assess their likelihood to produce hepatotoxicity via three mechanisms: bile acid transporter inhibition, mitochondrial dysfunction, and ROS production
- Liver exposure of each compound was predicted using a PBPK model (not shown)

RESULTS

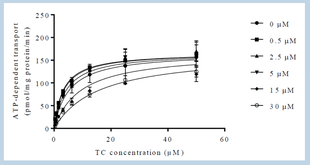
BSEP inhibition



Telcagepant



Ubrogepant

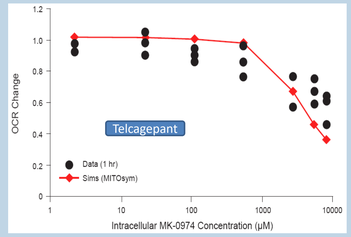


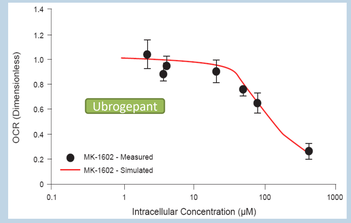
MK-3207

Left: BSEP inhibition was measured in a vesicle system for telcagepant (top), ubrogepant (middle), and MK-3207 (bottom). Mode of inhibition and K_i was determined due to the potential importance of this mechanism to the observed toxicity of telcagepant and MK-3207.

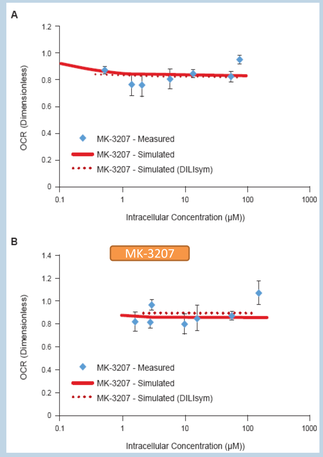
In Vitro Results

ETC inhibition



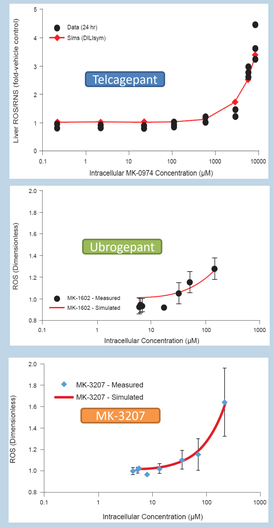


Mitochondrial toxicity data from HepG2 cells was fit using MITOsym, a model of *in vitro* mitochondrial bioenergetics (4); rate constants for ETC inhibition from MITOsym were converted to DILIsym parameters using a conversion factor.



ROS production

Right: Oxidative stress generation data in HepG2 cells for telcagepant (top), ubrogepant (middle), and MK-3207 (bottom) was fit in DILIsym using a simulated dosing protocol meant to mimic *in vitro* conditions. The rate constant that provided the best fit to these data was used in the simulations below.



Toxicity Parameters

The *in vitro* experimental results above are translated into DILIsym parameter values for use in the DILIsym simulations for each compound. These values should not be interpreted in isolation; rather, they serve as a snapshot of the model for each compound. For MRP3/4 and NTCP, the mode of inhibition was not determined experimentally; mixed inhibition with α = 5 was used as a baseline assumption due to experience with other transporter inhibitors.

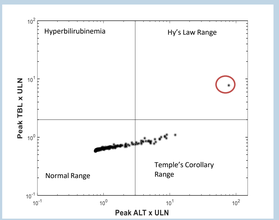
Mechanism	DILIsym Parameter	Unit	DILIsym Parameter Value		
			Telcagepant	MK-3207	Ubrogepant
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	μM	17,400	N/A	472
	Coefficient for ETC inhibition 3	μM	N/A	0.347	N/A
	Max inhibitory effect for ETC inhibition 3	dimensionless	N/A	0.35	N/A
Oxidative Stress	RNS/ROS production rate constant 1	mL/nmol/hr	2.0×10^{-5}	2.2×10^{-4}	1.6×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	μM	7.9	7.62	38.1
	BSEP inhibition alpha value	dimensionless	4.6	Competitive	8.39
	NTCP inhibition constant	μM	19.4	No Inhibition	No Inhibition
	MRP3/4 inhibition constant**	μM	16.6	49.9	85.9

Simulation Results

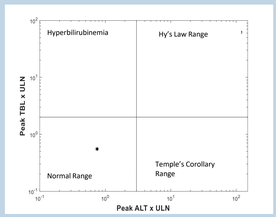
Compound	Dosing Protocol	Simulated* ALT > 3X ULN**	Clinical ALT > 3X ULN***
MK-3207, Competitive BSEP Inhibition, no RM	200 mg, 2 daily doses 2 hours apart (400 mg daily dose), for 14 days	3.5% (10/285)	42% (5/12) amongst individuals dosed for more than 1 week; most responding were given 600 – 900 mg per day
	300 mg, 2 daily doses 2 hours apart (600 mg daily dose), for 14 days	7% (20/285)	
	450 mg, 2 daily doses 2 hours apart (900 mg daily dose), for 14 days	10.2% (29/285)	
Telcagepant	280 mg BID 12 weeks	12.6% (36/285)	3.2% (8/265)
	140 mg BID 12 weeks	0% 0/285	1.9% (5/263)
Ubrogepant	100 mg q.d. for 8 days	0% (0/285)	Not known at time of simulation
	100 mg q2h (200 mg per day), 2 daily doses, for 4 days	0% (0/285)	
	100 mg q.d. for 2 days, 2 days off, 56 days total of dosing with 28 total doses	0% (0/285)	
	1000 mg q.d. for 8 days	0% (0/285)	

Simulations generally recapitulated the clinically observed toxicity for telcagepant and MK-3207. For ubrogepant, simulations predicted that the drug would be safe with a substantial safety margin of >10x the clinical dose.

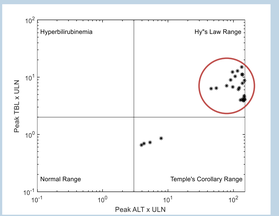
MK-3207 450 mg bid 14 days



Ubrogepant 200 mg split qd 4 days



Telcagepant 280 mg bid 12 weeks



CONCLUSIONS

- DILIsym correctly predicted the hepatotoxicity of telcagepant and MK-3207
- DILIsym prospectively predicted that ubrogepant would be safer than either telcagepant or MK-3207
- Clinical trials completed after the completion of this work supported the safety of ubrogepant; no liver signals were observed
- Ubrogepant has been approved by the FDA for the acute treatment of migraines.

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