Advancing Calcitonin Gene-Related Peptide Receptor Antagonists Using Quantitative Systems Toxicology Modeling to Characterize Next-in-Class Compounds Compared to the Hepatotoxic First in Class Telcagepant

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INTRODUCTION

While CGRP receptor antagonists have demonstrated efficacy in the acute and preventive treatment of migraine, two early CGRP signal-blocking compounds (gepants) showed liver injury signals in clinical trials. During clinical development of next-in-class gepants, confidence in compound safety was needed given the prior experience.

AIM

Biohaven enlisted DILIsym Services, Inc. (DSSI) to use DILIsym to independently assess the potential for liver toxicity to compare four next-in-class gepant compounds in clinical development to the hepatotoxic agent telcagepant.

MATERIAL & METHODS

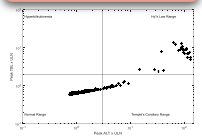
Models for telcagepant and four novel CGRP receptor antagonists (rimegepant, zavegepant, ubrogepant, and atogepant) were constructed in DILIsym v6A, a quantitative systems toxicology (QST) model of drug-induced liver injury. *In vitro* experiments were performed to measure the potential for each compound to inhibit bile acid transporters, produce oxidative stress, and cause mitochondrial dysfunction; physiologically-based pharmacokinetic (PBPK) models were produced for each compound to estimate liver exposure. Compounds were simulated at and above respective clinical dose regimens.

RESULTS

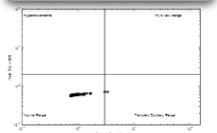
Telcagepant showed liver safety signals including: a) dose-dependent decrease in oxygen consumption rate (OCR) consistent with electron transport chain (ETC) inhibition, b) noncompetitive BSEP inhibition and c) liver exposure accumulation greater than in plasma resulting in an eDISH profile falling into Hy's Law range (see plots). Model-based elimination to identify the impact of contributors suggested synergy between bile acid accumulation and ETC inhibition as contributing to telcagepant toxicity. None of the other 4 novel gepants showed eDISH signals in Hy's Law range (see plots) and none showed simulated signals >1% frequency for ALT > 3X upper limit of normal (ULN) at clinical doses (see table). When clinical doses were exceeded only atogepant and ubrogepant showed simulated signals ≥10% frequency for ALT > 3X ULN. Simulations predicted rimegepant, zavegepant, atogepant, and ubrogepant would be safe at clinical doses.

RESULTS (cont'd)

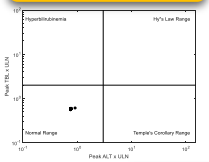
Telcagepant; 140 mg BID, 12 weeks, high ETCi



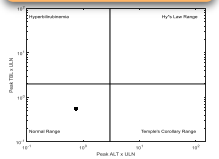
Rimegepant; 75 mg QD, alternate day dosing, 14 total doses over 28 days



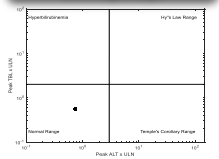
Atogepant; 60 mg BID, 12 weeks



Ubrogepant; 100 mg QD, 25 straight days



Zavegepant; 20 mg IN or 750 mg PO or 7.5 mg IV, 25 straight days



Compound	Oral Dosing Protocol	Simulated* ALT > 3X ULN	Observed ALT > 3X ULN in Clinic
Telcagepant – Original ETC	140 mg BID, 12 weeks	17.5% (50/285)	1.9% (5/263)
	280 mg BID, 12 weeks	76.1% (217/285)	3.2% (8/265)
Telcagepant – Alternate ETC	140 mg BID, 12 weeks	0.0% (0/285)	1.9% (5/263)
	280 mg BID, 12 weeks	7.72% (22/285)	3.2% (8/265)
Rimegepant	75 mg QD, alternate day dosing, 14 total doses	0.35% (1/285)	--
	75 mg QD, 5 days on, 1 day off, 25 total doses	0.7% (2/285)	--
	75 mg QD, daily dosing for 25 days, 25 total doses	1% (3/285)	--
Zavegepant	750 mg oral QD, 25 days, 25 total doses	0.0% (0/285)	
	7.5 mg IV QD, 25 days, 25 total doses	0.0% (0/285)	
Atogepant	60 mg BID, 12 weeks	0% (0/285)	
	300 mg BID, 12 weeks	0.3% (1/285)	
	600 mg BID, 12 weeks	10.2% (29/285)	
Ubrogepant	100 mg QD, 25 days	0% (0/285)	
	500 mg QD, 25 days	1.4% (4/285)	
	1000 mg QD, 25 days	11.6% (33/285)	

*In vitro experiments led to the parameterization of each of the five CGRP compounds within DILIsym, with an alternate parameterization for telcagepant based on uncertainty in the *in vitro* data.

CONCLUSION

DILIsym correctly predicted the DILI liability of the first generation compound telcagepant. The four next-in-class compounds did not show the same signal for liver safety concerns as telcagepant. Subsequent clinical trials have validated these results, with rimegepant, ubrogepant and atogepant all approved by the FDA with no black-box warning for hepatotoxicity. Zavegepant continues in late-stage development. This work demonstrates the potential for QST modeling to prospectively differentiate between hepatotoxic and non-hepatotoxic molecules within the same class.

ACKNOWLEDGEMENTS

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REFERENCES

1. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. Cephalalgia Int J Headache. 2016 Feb;36(2):148–61.

DISCLOSURES

Drs. Woodhead, Siler, and Howell are employees of DILIsym Services, Inc., developers of DILIsym. Dr. Conway is employed by Biohaven, developers of rimegepant and zavegepant.

CONTACT INFORMATION

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