Lixivaptan, a vasopressin-2 receptor antagonist, is under development for the treatment of autosomal dominant polycystic kidney disease (ADPKD), an orphan disease with minimal treatment options. Tolvaptan, another vasopressin-2 receptor antagonist, is FDA approved to slow the progression of ADPKD but has produced liver safety signals. We prospectively compared the potential for lixivaptan versus tolvaptan to cause liver toxicity.

Methods

Simulations characterize separation between lixivaptan and clinical PK data

Conclusions

The potential toxicity of lixivaptan and its major metabolites were evaluated in DILIsym, a QST software for predicting drug-induced liver injury. DILIsym integrates:

- In vitro data on lixivaptan-induced oxidative stress, mitochondrial dysfunction, and inhibition of bile acid transporters
- Clinical PK data
- Interindividual variability

Lixivaptan simulation results compared with previously published tolvaptan simulation results (1).

Acknowledgements

- Palladio Biosciences, Inc.
- The members of the DILI-sim Initiative

References


Introduction

PBPK Parameterization using clinical PK data

Parameterization using in vitro data

Toxicity parameter values for lixivaptan and major metabolites

Oxidative Stress

Mitochondrial dysfunction

BSEP inhibition

DILIsym parameter values identified from in vitro data

Illustrative fits shown

Complete set of DILIsym input parameter values shown below

PBPK Parameterization using clinical PK data

The PBPK representation for lixivaptan and its metabolites was constructed with clinical data from Phase I trial results (n = 67) for seven-day 100 mg BID and 400 mg BID dosing regimens. Simulated liver concentrations consistent with rat WBAR data and in vitro intracellular measurements.

Results

- Simulations predict no clinically significant ALT elevations with lixivaptan
  - Contrasts with simulated and observed tolvaptan ALT elevations (1, 2)
  - Difference in simulation time (12 vs. 24 weeks) did not account for difference (results not shown)

- Intended clinical dose falls below exposure range for simulated ALT elevations
  - Lixivaptan simulations with 400 mg, BID for 7 days predict a correlation between exposure and response
  - Mechanism of toxicity differs between lixivaptan and tolvaptan

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Quantitative Systems Toxicology (QST) Supports Differentiated Liver Safety for a Next-in-Class Compound

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**Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications.**

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**Basolateral inhibition constant represents the lowest IC50 value of the experimentally derived MRP3 and MRP4 IC50 values.

*IC50 values; default assumption is mixed inhibition type with respect to clinical implications. Their predictive value resides in the combination with exposure in the context of a DILIsym simulation.