Assessing the Role of Quantitative Systems Pharmacology Modeling in Early Stage Drug Development for Urea Cycle Disorders

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Introduction

- Urea cycle disorders (UCDs) are rare genetic diseases with a deficiency of one of the six enzymes in the urea cycle. UCDs can result in hyperammonemia causing irreversible brain damage and death.
- The onset and severity of UCDs is highly variable and depends on the amount of residual function of the urea cycle enzymes. Metabolic stressors may trigger events in patients with mild to moderate UCDs, potentially causing severe neurological symptoms.
- Development of therapies for UCD is complex due to the different role played by each urea cycle enzyme, gaps in the understanding of disease pathophysiology and high patient variability.
- Quantitative systems pharmacology (QSP) modeling can enable the development of therapies for UCD and other rare diseases by addressing these challenges and providing mechanistic insight to support decision making.

Methods

A quantitative metabolic PhysioPD™ Research Platform was used as the basis for the UCD Platform development.

- A Urea Cycle Disorder PhysioPD™ Platform was developed to test potential drug treatments that affect the metabolism of amino acids (AA), ammonia, and urea. Rosa modified an existing PhysioPD™ Research Platform for this project. Urea and ammonia metabolism in the liver, kidney, and blood were incorporated into the original Research Platform that contained a quantitative mechanistic model of glucose, amino acid, and protein metabolism. The Platform included food intake with digestion and absorption of protein and amino acids.
- Pharmacokinetic representations for select AA transport inhibitor (SAATi) drugs were added to the Platform.
- Virtual Patients (VP) were created to simulate the physiology of an adult male with late onset ornithine transcarbamylase (OTC) deficiency, a representation of the UCD disease state. Changes in plasma ammonia and glutamine were evaluated after four weeks of simulated treatment with different hypothetical treatments, including restricted protein diets and a variety of SAATi.
- Based on the initial simulation results, an additional nine hypotheses were developed to explain the perceived discrepancies between simulations and preclinical data. Seven of these were evaluated further within the Platform. This hypothesis testing enabled the prioritization of experimental work to evaluate sensitive uncertainties.
- The Platform was qualified in accordance with Rosa’s Model Qualification Method (MQM) (Figure 1).

Results

A UCD PhysioPD Platform was developed and qualified.

- Platform qualification included comparison to preclinical and clinical data, including dietary and drug interventions. Diet interventions included response to fasting, oral glucose tests, and meal tests. Drug interventions included sodium phenylbutyrate (sodium PBA), arginine/citrulline, and a hypothetical ammonia (NH4+) binder.

Inhibition of AA absorption lowers plasma levels of ammonia and excess glutamine.

- A severe UCD VP was simulated with either standard or restricted protein diets and/or SAATi treatment. A second experiment simulated a hypothetical ammonia binding drug. The amount of glutamine above a healthy concentration was counted as excess.
- The simulated treatments resulted in decreased ammonia production which may contribute to declines in plasma ammonia concentration.

Co-administration of an AA transport inhibitor with citrulline reduces plasma ammonia.

- A UCD VP was simulated with no treatment, SAATi, citrulline, or combination of SAATi and citrulline.
- Simulations suggest that adding citrulline allows the urea cycle to pull ammonia from the plasma ammonia pool, excrete it and lower ammonia concentrations.

Conclusions

- Research conducted in the UCD Platform provided guidance to support more definitive preclinical experimental design and compound evaluation.
- In addition, the research identified two therapeutic approaches that would combine well with a SAATi target.
- Quantitative modeling facilitated the development and testing of hypothetical drug targets in early-stage drug development.

References


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