SIMD Annual Meeting, 18 Mar – 21 Mar 2023, Salt Lake City, UT, USA
Abstract submission deadline: 30 Nov 2022, 11:59 pm MST

A QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODEL FOR CLASSICAL HOMOCYSTINURIA PREDICTING EFFICACY OF TREATMENT

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ABSTRACT

Background: Classical homocystinuria (HCU) is a rare metabolic disorder of the methionine (Met) catabolic pathway, in which lack of cystathionine β-synthase (CBS) leads to excessive accumulation of homocysteine (Hcy) and other metabolic abnormalities causing strokes, ocular and cognitive impairment, and skeletal abnormalities. The current standard of care is dietary protein restriction with Met-free formula, pyridoxine, and betaine (Bet), but its therapeutic impact is limited. Pegtibatinase is a recombinant human enzyme replacement therapy designed to reduce excessive Hcy buildup in plasma and consequently in tissues. A QSP model of pathological Met metabolism due to loss of CBS activity was established to simulate the global effects of pegtibatinase, with and without dietary modifications and Bet supplementation, on plasma Hcy and other sulfur amino acid metabolites in patients with HCU.

Methods: A QSP model was constructed to predict the plasma and tissue concentrations of Hcy, cysteine (Cys), Met, S-adenosylmethionine (SAM), S-adenosylhomocysteine, Bet, and cystathionine. The remethylation and transsulfuration pathways were integrated into a whole organism model. The model considered differences in enzyme expression in the brain, liver, and kidney; the oxidized forms of Cys and Hcy in plasma; dietary uptake of Met and Cys; Bet supplementation; and the biodistribution of amino acids.

Results: Our HCU QSP model reproduced most of the plasma and tissue metabolite steady-state measurements in the full *CBS* knockout (KO) and transgenic I278T mouse models where dietary Met was fed *ad libitum*. In I278T mice, the model predicted strong buffering of tissue and plasma Met, even with elevated Hcy, because of positive allosteric feedback on Met adenylation by SAM, but it predicted a proportional relationship between Hcy and Met in neonatal, full KO mice where negative instead of positive feedback exists on Met adenylation. The model successfully simulated the short-term efficacy of pegtibatinase in I278T mice under Met-restricted diet (MRD). Simulations of MRD (Met reduced by 50%–87.5% of normal intake) predicted 11%–81% decreases in plasma Hcy. Pegtibatinase along with Bet supplementation normalized plasma total Hcy on MRD. Both modelling and mouse data show that pegtibatinase was more effective in lowering plasma total Hcy than Bet supplementation and/or moderate dietary restriction without risk of hypermethioninemia due to Bet supplementation. This suggests that relaxation or cessation of dietary modifications and Bet supplementation may be possible with pegtibatinase therapy. The QSP model can be allometrically scaled and updated with human gastrointestinal physiology to analyze results from an ongoing HCU Natural History Study and the Phase 1/2 COMPOSE study.

Conclusions: This QSP model provides significant insights into the complex pharmacology of pegtibatinase and the pathophysiology of HCU. The model explains sulfur amino acid metabolism in plasma and tissues in mouse models

of HCU under steady-state, dietary modifications, and treatment with pegtibatinase. The model suggests that pegtibatinase is more effective in controlling Hcy levels than Bet supplementation, especially for less restrictive diets. Using clinical HCU data, the model will assist in predicting the optimal dosing regimen to effectively reduce plasma Hcy levels on less restrictive diets without Bet supplementation.

Disclosures:
TM: Ad hoc consultant for Travere; Inventor on patents related to pegtibatinase
RM: QSP consultant for Travere Therapeutics
MK: QSP consultant for Travere Therapeutics
PHvdG: QSP consultant for Travere Therapeutics
DC: QSP consultant for Travere Therapeutics
YC: Travere employee
SR: Travere employee
KL: Travere employee