The Impact of Ribavirin Plasma and Cellular Pharmacokinetics and Host Genetics on Anemia and Antiviral Response to Hepatitis C Treatment

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Objectives: To develop a model relating ribavirin systemic and intracellular exposure [1] to toxicity (anemia) and drug response (viral load) as a basis for guiding a more precise treatment of HCV with ribavirin.

Methods: The study [1] enrolled 36 subjects: 18 received pegylated interferon alfa (Peg-IFN \(\alpha\)) and ribavirin, 18 received Peg-IFN \(\alpha\), ribavirin, and telaprevir. The model framework consisted of a systemic pharmacokinetic model of ribavirin, a cellular phosphorylation model in peripheral blood mononuclear cells (PBMC) and red blood cells (RBC), a ribavirin-induced anemia (toxicity) model and a viral dynamic (efficacy) model. Potential covariates considered were the effect of telaprevir use, age, weight, sex, creatinine clearance, and inosine triphosphatase (ITPA) and interferon lambda 3 (IL28B) genetics. The analysis was performed using the maximum likelihood, expectation maximization (MLEM) algorithm in ADAPT 5.

Results: Ribavirin-induced anemia was described by an indirect response model with ribavirin triphosphate exposure in RBC stimulating the loss rate of RBC. The feedback effect of endogenous erythropoietin was included through regulation of the RBC production rate (\(R_{in} [\frac{Hb_0}{Hb}]^\gamma\)). Individuals receiving telaprevir, with wild-type ITPA genetics and IL28B CC genotype were most likely to experience anemia. The 2-equation viral dynamic model [2] was improved by incorporating the better treatment efficacy associated with the co-administration of telaprevir and IL28B CC genotype.

Conclusions: We have utilized quantitative systems modeling approaches to link ribavirin exposure to hemoglobin reduction and viral response, as well as the influence of pharmacogenetic and clinically relevant covariates on these processes. Simulations showed the utility of this model framework to investigate alternative treatment strategies to minimize the incidence of anemia associated with ribavirin treatment.

References: