A population model for respiratory syncytial virus (RSV) kinetics using transit compartments based on human challenge data

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Objectives: Respiratory syncytial virus (RSV) causes acute respiratory tract infections, and is a major cause of hospital admissions and death in young children world-wide. Currently, no effective treatments exist in adults or children. The aims of this work were to develop a pharmacometric model describing the viral kinetics of RSV, to describe the impact of drug treatment and to determine the relationship between viral load and symptom scores.

Methods: A target-cell limited viral kinetics model with delayed virus production developed by Baccam et al. for influenza A infections (1) is commonly used to describe RSV kinetics. The transit compartment model that best described the placebo data was carried forward into the PKPD model development for the investigational fusion inhibitor. Model development was conducted in NONMEM 7.3 using the SAEM estimation algorithm followed by importance sampling.

Results: The best placebo model included four transit compartments for infected, non-producing cells, and a single compartment for producing cells. This model fitted the placebo data significantly better than the prior model (1). Between-subject variability was included on the infection rate constant and virus production rate constant, and was found to be high (>200%), with a significant negative correlation (Pearson’s Correlation Coefficient = -0.97). The effect of treatment with the fusion inhibitor on RSV kinetics in nasal lavage was best described by a non-dose dependent transformation of the infectious virions into a non-infectious state. A proportional odds model was used for describing symptoms scores with viral loads as predictor.

Conclusions: An extended target-cell limited viral kinetics model with delayed virus production using a series of transit compartments was successfully applied to describe the viral kinetics of RSV in nasal lavage and the impact of treatment with a fusion inhibitor in a human challenge model.

References: