Modeling the Impact of Antidrug Antibody Formation on the Pharmacokinetics of a Fully Human Monoclonal Antibody in a Preclinical Rodent Model

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Objective: The objective of this study is to assess the time course and extent of ADA formation and its impact on the PK profile after administration of a human monoclonal antibody at differing dose levels and with different immunomodulation strategies in rats.

Methods: A human IgG2 monoclonal antibody (mAb1), without target binding in rats, was dosed at three different levels: 0.01, 50 and 300 mg/kg weekly in Sprague Dawley rats for 4 weeks. Within each dose level, three immunomodulation strategies were used. One group was administered mAb1 alone. The second group was administered mAb1 and an immunosuppressive regimen of rapamycin (6 mg/kg) at the beginning of the study and tacrolimus (2 mg/kg) weekly. The third group was administered mAb1 and methotrexate (5 mg/kg) in 3 consecutive doses on days 0, 1 and 2. Blood samples were drawn from the tail vein at predetermined time points and analyzed for mAb1 concentrations and the presence of ADA. Population PK modeling of the mAb1 concentrations and ADA effect was performed using nonlinear mixed effects modeling (NONMEM).

Results: mAb1 serum concentrations were best described by a two-compartment model. The formation of ADA increased clearance for mAb1 and ADA signal-to-noise ratio was incorporated into the model using a modifier for clearance of \((1+(\text{ADA} \times \text{SN})^{\text{ANTI}})\), where ADA signals the presence of antidrug antibody in the sample, SN is the signal-to-noise ratio measured in that sample and ANTI is the estimate of the ADA effect on clearance. The point estimates were the following: clearance 0.000433 l/h/kg; absorption rate constant 0.00360 h\(^{-1}\), volume of distribution of the central compartment 0.0866 l/kg, inter-compartmental clearance 0.000100 l/h/kg and effect of ADA on clearance 1.57.

Conclusions: This study and model illustrate the substantial impact of ADA formation on the clearance of therapeutic proteins when compared to animals without an immune response.