A PK model to predict the impact of antibody enhancement technologies

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Objective: Although most antibodies effectively neutralize their cognate antigens, some of them have to be dosed at high frequency or high dose in order to obtain therapeutic efficacy, often based on the high target level and/or antigen-mediated degradation of the antibody. Novel antibody enhancement technologies have been described in the literature and aimed to significantly increase the exposure of the antibody, allowing greater flexibility of dosing frequency and route of administration [1,2]. The objective of this work was to build a PK model that could be used to describe the circulating level of an antibody under normal conditions and to predict its level when the system was modulated by various antibody enhancement technologies such as pH switch or FcRn binding increase.

Methods: Clinical pharmacokinetic data were incorporated into a PK model of antibody-target binding, using typical IgG characteristics [3], turnover of the target and measured *in-vitro* binding affinity. The model was then adjusted to include a pH-dependent change in binding affinity for both target or binding of antibody to FcRn. The final model was used to predict blood IgG levels in human and other species across various dosing regimens and various level of impact of the enhancement techniques. The model was coded in ordinary differential equations and the simulations were performed in Berkeley Madonna software.

Results: The PK model was a two-compartment model including a 1 to 1 binding process between the antibody and its target in the central compartment and in quasi equilibrium conditions [4]. The transfer from central to peripheral compartment was assumed to be passive. The validity of the model was supported by successful simulations of published preclinical data for two monoclonal antibodies exhibiting target-mediated drug disposition: Tocilizumab [2] and anti-PCSK9 antibody [1].

The PK simulations in human for an antibody with target-mediated drug disposition demonstrated that pH-switch technology had the biggest impact on extending half-life by 3 to 4 fold, whereas the impact of FcRn binding enhancement alone had no benefit.

Conclusions: Incorporation of fundamental biological principles and clinical data into a combined model of antibody-target binding, coupled with novel antibody enhancement strategies, allowed the prediction of clinical utility of pharmacological potential of certain therapeutic approaches.

References:

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