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Quantitative prediction of therapeutic antibody pharmacokinetics after intravenous and subcutaneous injection in human

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ABSTRACT

Prediction of the plasma/serum mAb concentration–time profile in human is important to determine the required dose regime. This study proposes an approach for predicting the plasma/serum mAb concentration–time profile after intravenous and subcutaneous injection in human based on comprehensive analysis of reported pharmacokinetic data. Optimal scaling exponents from cynomolgus monkey to human for CL, Q, V_c, and V_p were estimated as 0.8, 0.75, 1.0, and 0.95, respectively. The estimated exponents were used to predict plasma/serum mAb concentration–time profile in human from pharmacokinetic data in cynomolgus monkey, and the results had reasonable accuracy with symmetric variability of prediction. Then, data reported for pharmacokinetics in human were used to estimate optimal k_a and F after subcutaneous injection. The geometric mean of k_a was suitable to predict T_{max}, and F which was estimated from CL was suitable to predict C_{max}. Our approach is useful for predicting the plasma/serum mAb concentration–time profile after intravenous and subcutaneous injection in human. Moreover, the study also investigated the possibility of predicting pharmacokinetic parameters of mAbs with increased FcRn binding mutations in human and found that our approach of prediction based on reported pharmacokinetic data may also be applicable to mAbs with these mutations.

1. Introduction

The prediction of pharmacokinetics in human is important in drug development because pharmacokinetics has a great impact on dose and dose regime in the clinical situation. Generally, *in vivo* animal data and/or *in vitro* data is used to determine the dose for first-in-human studies, and several approaches to predict pharmacokinetics in human have been reported [1,2]. To predict the pharmacokinetics in human of therapeutic antibodies (mAbs), several groups have reported the use of the allometric scaling approach based on pharmacokinetic data in cynomolgus monkey [3–6]. These studies reported that the allometric scaling approach can accurately predict clearance (CL) and volume of distribution at steady state (V_{ss}) of mAbs in human from pharmacokinetic data in cynomolgus monkey.

It has been reported that FcRn plays an important role in the rescue of immunoglobulin G (IgG) from endosome to cell surface [7,8]. This recycling system of IgG by FcRn provides IgG-based mAbs with superior half-life in animals and human compared with small molecular drugs and other protein drugs, such as erythropoietin [9] and coagulation factor VIII [10]. IgG-FcRn binding is known to be pH-dependent, which means that IgG binds to FcRn very weakly at neutral pH (KD > 10,000 nM), but binds to FcRn at acidic pH (pH 5–6) (KD: 1000–2000 nM) [11]; in other words, IgG binds to cell surface FcRn in plasma very weakly, but binds to FcRn in acidic endosome, from whence it can be recycled to the cell surface and released to plasma fluid and interstitial fluid. To achieve low immunogenicity of mAbs in human, the human IgG sequence is used in the constant region of most of mAbs, and thus in preclinical studies the interaction of human IgG with human FcRn needs to be considered. Although the IgG-FcRn binding has been reported to have inter-species difference, the binding of human IgG to human FcRn is reported to be similar to the binding of human IgG to cynomolgus monkey FcRn [12]. Hence, using cynomolgus monkey to predict the pharmacokinetics of mAbs in human can be considered as appropriate.

Generally, mAbs show biphasic concentration–time profiles in plasma and in serum after intravenous administration in human [13] and animals [14], but these profiles cannot be described using only CL and V_{ss}. Therefore, the two-compartment model has been

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commonly used to describe these profiles [15,16] by estimating four parameters: CL, inter-compartmental clearance (Q), volume of distribution in the central compartment (V_c), and volume of distribution in the peripheral compartment (V_p). These four parameters are needed to understand mAbs pharmacokinetic profiles quantitatively and to conduct pharmacokinetics/pharmacodynamics (PK/PD) analysis of mAbs [17,18]. Although several mechanistic models that incorporated tissue elimination and endosomal recycling have been reported [19,20], the two-compartment model is the one most often used to describe the biphasic pharmacokinetics of mAbs and would be sufficient to predict pharmacokinetics in plasma or in serum. However, an approach using two-compartment model parameters to predict the pharmacokinetics of mAbs in human has not been reported.

Subcutaneous injection is generally seen as the appropriate route when treating chronic disease with mAbs because it is more convenient for patients and also hospitals. Although intravenous infusion requires the use of a bed for 30 min or a few hours, subcutaneous injection does not require a bed and, moreover, in some cases can be done at home. To decide the dose and frequency of subcutaneous injection in the clinical situation, it is essential to understand the pharmacokinetics of mAbs by that route in human, but so far no methodology for predicting the adsorption rate constant (k_a) and bioavailability (F) in human has been established.

In this study, the reported pharmacokinetics data of mAbs in cynomolgus monkey and human are comprehensively analyzed. First, we propose using the allometric scaling approach to predict two-compartment model parameters in human from pharmacokinetic data in cynomolgus monkey. Then, we propose predicting the mAb concentration–time profile after subcutaneous injection in human plasma and serum using the allometric scaling approach and reported subcutaneous pharmacokinetic data of mAbs in human. Moreover, the possibility of predicting two-compartment model parameters in human of mAbs that have mutations that increase the FcRn binding was also addressed.

2. Materials and methods

2.1. Data collection

Pharmacokinetic data of mAbs in human and cynomolgus monkey were obtained from literature, patents, presentations at scientific conferences, or information from the Pharmaceutical and Medical Devices Agency (PMDA) and Food and Drug Administration (FDA). If body weight information was not available, body weight of 3 kg (cynomolgus monkey) and 75 kg (human) was applied. Generally, pharmacokinetic data on mAbs concentration in plasma and serum is available. In this study, pharmacokinetics data on mAbs concentration in serum was assumed to be the same as that in plasma. The average values of pharmacokinetic parameters and mAb concentration–time profiles in plasma or serum in cynomolgus monkey and human were collected from published data. These mAb concentration–time profiles were scanned to obtain pharmacokinetic parameters by two-compartment model analysis and/or confirm the predictability of our approach. mAbs that show linear pharmacokinetics were selected as the data source, because nonlinear pharmacokinetics requires a more complex model to capture the profiles. If multiple data sources were available, data on the highest dose was selected as the data source.

2.2. Two-compartment model analysis

If published data provided two-compartment model parameters, these values were used. If these parameters were unavailable, the mAb concentration–time profiles were analyzed using the traditional two-compartment model with first order elimination to estimate the parameters CL, Q, V_c, and V_p. The profiles were fitted to the following equation,

$$C = A \times e^{-\alpha \times t} + B \times e^{-\beta \times t}$$

and each parameter was obtained according to the following equations.

$$\alpha + \beta = k_{12} + k_{21} + k_{el}$$

$$\alpha \times \beta = k_{21} \times k_{el}$$

$$\beta = \frac{1}{2} \times \left[(k_{el} + k_{12} + k_{21}) - \sqrt{(k_{el} + k_{12} + k_{21})^2 - 4 \times k_{el} \times k_{21}} \right]$$

$$V_c = \frac{Dose}{A + B}$$

$$CL = k_{el} \times V_c$$

$$Q = k_{12} \times V_c$$

$$V_p = \frac{V_c \times k_{12}}{k_{21}}$$

k_{el}, k_{12}, k_{21} represent the elimination rate constant, the distribution rate constant from the central to the peripheral compartment, and the distribution rate constant from the peripheral to the central compartment, respectively.

2.3. Allometric scaling

The CL (mL/day), Q (mL/day), V_c (mL), and V_p (mL) in human were extrapolated from pharmacokinetic data in cynomolgus monkey using the allometric scaling equation, with the scaling exponents of each parameter calculated using the following equations.

$$CL_{human} = CL_{monkey} \times \left(\frac{BW_{human}}{BW_{monkey}} \right)^{e_{CL}}$$

$$Q_{human} = Q_{monkey} \times \left(\frac{BW_{human}}{BW_{monkey}} \right)^{e_{Q}}$$

$$V_{c,\,human} = V_{c,\,monkey} \times \left(\frac{BW_{human}}{BW_{monkey}} \right)^{e_{V_c}}$$

$$V_{p,\,human} = V_{p,\,monkey} \times \left(\frac{BW_{human}}{BW_{monkey}} \right)^{e_{V_p}}$$

Respectively, BW and e represent body weight and scaling exponent. To estimate the optimal exponents for CL, Q, V_c, and V_p, the predictability of CL, Q, V_c, and V_p in human was evaluated using several exponents.