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Allometric Scaling of Therapeutic Monoclonal Antibodies Using Antigen Concentration as a Correction Factor: Application to the Human Clearance Prediction

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ABSTRACT

Allometric scaling has been widely used for predictions of human pharmacokinetic (PK) parameters in the development of monoclonal antibody (mAb) drugs, and some correction factors have been proposed to improve the estimations. However, classic correction factors fail to offer a complete explanation of the additional differences among species besides the body weight and, thus, lack enough power to further improve the predictions. In this study, the antigen concentration was initially set as a new correction factor to predict the human clearance (CL) of mAbs. Bevacizumab was intravenously injected into 2 animal species and humans to obtain PK data to predict human CL from the animal data. Additionally, a new approach was also validated with data from 3 other mAbs which were collected through a literature review of published work. Accordingly, allometric scaling with a correction factor of the antigen concentration generated accurate estimations of the human CL of 4 mAbs, which were superior to the results obtained by other classic scaling methods. More importantly, the proposed method also achieved good predictions of individual human CL of bevacizumab. In conclusion, the potential of this method as a powerful tool for human PK estimation of mAbs in species translation has been demonstrated.

Introduction

Prediction of human pharmacokinetic (PK) profiles plays an important role in drug development, especially before the first-in-man studies, regarding dosing regime, efficacious dose, and commercial viability.[1] In recent years, more and more monoclonal antibodies (mAbs) have been approved as therapeutic drugs and used in the clinic for various diseases, such as cancer, inflammatory diseases, and hematological disorders.[2,3] A prediction of human PK properties of mAbs from preclinical data supports an early assessment of their potential value in drug development.[4]

Allometric scaling is the fundamental and most widely used approach for the prediction of interspecies PK parameters based on the assumption that anatomic, physiological, and biochemical similarities exist among species. In fact, PK parameters vary across species as a function of body weight (BW) in terms of a simple allometric equation $Y = a \cdot BW^b$, where Y is the parameter of interest, BW is body weight, a is the allometric coefficient, and b is the allometric exponent.[5] Allometric scaling should achieve an accurate prediction of mAb PK parameters if the interspecies differences can be determined by BW alone. However, PK scaling across species with simple allometric equation fails in some cases including nonlinear PK, qualitative and quantitative differences in disposition pathways, and so forth.[6] To improve the predictions, 2 approaches that add a correction factor to simple allometric equation are developed as follow: (1) the product of the CL and the maximum life span potential (MLP) versus the BW and (2) the product of the CL and the brain weight (BrW) versus the BW. Those correction factors including the MLP and BrW are applied to elucidate additional PK differences among species.[7] They have been shown to be applicable to some mAbs when linear PK across species is presented.[8]

Abbreviations used: AC, antigen concentration; ADCC, antibody-dependent cellular cytotoxicity; BrW, brain weight; CL, clearance; mAb, monoclonal antibody; MLP, maximum life span potential; NCA, noncompartmental analysis; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

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It is well established that mAbs play their pharmacologic role by specifically binding to their antigens, such as some cytokines and receptors, to inhibit the pathologic effects of the antigens. Binding to the antigens in turn triggers antibody-dependent cellular cytotoxicity (ADCC) and/or complement activation to induce the elimination of mAbs.[9,10] Thus, the PK profiles of mAbs will be affected by their antigens through a target-mediated drug disposition, and additional PK differences are exhibited accordingly. In addition, the expression of antigens varies among species, and it is also sensitive to disease development and individual variations.[11] Antigen level should thus be another important factor affecting interspecies and even individual PK of mAbs. Although some successful predictions of human CL of mAbs have been accomplished by correcting the allometric equation with MLP and BrW, those 2 classic correction factors cannot correct the additional PK differences caused by target-mediated elimination because they fail to reflect the variations of *in vivo* antigen concentration (AC).[1] In such a case, AC may be a more suitable correction factor to determine the additional interspecies PK differences when applying the allometric scale for PK parameters of mAbs.

In this work, the AC was initially set as a factor to correct the allometric scaling equation for human CL estimation of 4 types of mAbs, including bevacizumab, etanercept, infliximab, and adalimumab. More importantly, individual human CL of bevacizumab was also predicted from preclinical data using this new approach.

Methods

Allometric Scaling

Simple Allometric Scaling

CL of the mAbs in each species was plotted against the BW on a log-log scale in accordance with the allometric equation as follows:

$$CL = a \cdot BW^b \quad (1)$$

Where a is the allometric coefficient and b is the allometric exponent. If no specific BW information was available in the actual study, BWs of 250 g (rat), 3.5 kg (monkey), and 70 kg (human) were used.

Allometric Scaling With Correction Factors of MLP or BrW

CL of the mAbs in each species was multiplied by the MLP or BrW (Eqs. 2 and 3) of the species, and then the product was plotted as a function of BW on a log-log scale.

$$MLP \cdot CL = a \cdot BW^b \quad (2)$$

$$BrW \cdot CL = a \cdot BW^b \quad (3)$$

MLP and BrW were calculated as previously described.[12]

Allometric Scaling With Correction Factor of AC

The CLs of the mAbs in each species were divided by the AC (Eq. 4) of the species, and then the product was plotted as a function of BW on a log-log scale.

$$CL/AC = a \cdot BW^b \quad (4)$$

The AC data of vascular endothelial growth factor (VEGF, the antigen of bevacizumab) were detected by enzyme-linked immunosorbent assay (ELISA) kits in our laboratory and that of tumor necrosis factor α (the antigen of various mAbs, including etanercept, infliximab, and adalimumab) were collected from published work.

Allometric Scaling of Human CL

In the predictions of the human CLs of 4 mAbs, the mean CLs and the mean physiological parameters of different animal species were used to calculate the average level of the human CLs. Regarding individual human CL, each value was scaled with the mean CLs of different animal species and the individual physiological parameters as described in the previous equations.

Bevacizumab PK Studies in Rabbits, Dogs, and Healthy Human Volunteers

Materials

Bevacizumab (Avastin, 100 mg/4 mL) was purchased from the manufacturer (Genentech, San Francisco, CA). Recombinant human $VEGF_{165}$ (Peprotech) was immobilized on solid phase surface of 96-well plates (Greiner, Germany) to capture the bevacizumab. Five percent nonfat dried milk (Dingguo Changsheng Biotechnology, China) dissolved in phosphate-buffered saline (PBS) (Dingguo Changsheng Biotechnology, China) was used to seal the solid phase surface of each well and 0.5% Tween-20 (Damao Chemical Reagent Factory, China) in PBS was used as a wash solution. Horseradish peroxidase-goat anti-human IgG (H+L) conjugate (ABclonal Technology, UK) was used to detect bevacizumab. Tetramethyl benzidine (Solarbio, China) and 1 mol/L sulfonic acid (Sinopharm Chemical Reagent, China) were prepared in the laboratory and used as substrate solution and stop solution, respectively.

Animals

The animal studies were approved by the animal ethics committee of the Third Xiangya Hospital of Central South University. All experiments were conducted in accordance with the National Institute of Health guideline for the care and use of laboratory animals.

Fourteen New Zealand rabbits comprising 7 males and 7 females, weighing between 1.7 and 2.5 kg, and 11 beagle dogs comprising 6 males and 5 females, weighing between 7.1 and 11.2 kg, were obtained from Slac Jingda Laboratory Animal Co., Ltd. (Changsha, China) and Rixin Technology Co., Ltd. (Beijing, China), respectively. All animals were kept under a 12-h light-dark cycle at an ambient temperature of 21°C-22°C, and unlimited access to standard laboratory diet and water.

Healthy Volunteers

This study was approved by the ethics committee of the School of Pharmaceutical Sciences of Central South University (Changsha, China). Written informed consent was obtained in accordance with the good clinical practice guidelines published by the State Food and Drug Administration of China.

Six Chinese healthy volunteers including 4 male and 2 female, between 20 and 23 years old and with a weight range from 49 to 69 kg, were enrolled to receive single-dose injections of bevacizumab. Exclusion criteria included any clinically significant medical history or physical findings; presence of pregnancy or lactation; blood or blood product donation within 30 d of medication administration; serious disease of the heart, liver, kidney, or endocrine system; prior anti-VEGF therapy; infection (acute or chronic); HbsAg-positive status; HIV; and a history of tuberculosis or a positive tuberculosis skin test; psychosis, emotional, or intellectual problems likely to limit the validity of the consent; or previous receipt of bevacizumab.

Blood Sampling

The rabbits were randomly divided into 2 groups among which no significant difference existed with respect to BW and sex and then received an intravenous infusion treatment of 15 mg/kg and 5