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Clinical Pharmacokinetics

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ORIGINAL RESEARCH ARTICLE

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A Guide to Rational Dosing of Monoclonal Antibodies

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Abstract

Background and Objective: Dosing of therapeutic monoclonal antibodies (mAbs) is often based on body size, with the perception that body size-based dosing would reduce inter-subject variability in drug exposure. However, most mAbs are target specific with a relatively large therapeutic window and generally a small contribution of body size to pharmacokinetic variability. Therefore, the dosing paradigm for mAbs should be assessed in the context of these unique characteristics. The objective of this study was to review the current dosing strategy and to provide a scientific rationale for dosing of mAbs using a modelling and simulation approach.
Methods: In this analysis, the body weight-based or body weight-independent (fixed) dosing regimens for mAbs were systematically evaluated. A generic two-compartment first-order elimination model was developed. Individual or population pharmacokinetic profiles were simulated as a function of the body weight effects on clearance (θ_{BW_CL}) and on the central volume of distribution (θ_{BW_V1}). The variability in exposure (the area under the serum concentration-time curve [AUC], trough serum concentration [C_{min}] and peak serum concentration [C_{max}]) was compared between body weight-based dosing and fixed dosing in the entire population. The deviation of exposure for light and heavy subjects from median body weight subjects was also measured. The simulation results were then evaluated with clinical pharmacokinetic characteristics of various mAbs that were given either by body weight-based dosing or by fixed dosing in the case study.
Results: Results from this analysis demonstrated that exposure variability was dependent on the magnitude of the body weight effect on pharmacokinetics. In contrast to the conventional assumption, body weight-based dosing does not always offer advantages over fixed dosing in reducing exposure variability. In general, when the exponential functions of θ_{BW_CL} and θ_{BW_V1} in the population pharmacokinetic model are <0.5, fixed dosing results in less variability and less deviation than body weight-based dosing; when both θ_{BW_CL} and θ_{BW_V1} are >0.5, body weight-based dosing results in less variability and less deviation than fixed dosing. In the scenarios when either θ_{BW_CL} or θ_{BW_V1} is >0.5, the impact on exposure variability is different for each exposure measure. The case study demonstrated that most mAbs had little effect or a moderate body weight effect (θ_{BW_CL} and θ_{BW_V1} <0.5 or ~0.5). The difference of variability in exposure between body weight-based and fixed dosing is generally less than 20% and the percentages of deviation for light and heavy subpopulations are less than 40%.
Conclusions: The analysis provided insights into the conditions under which either fixed or body weight-based dosing would be superior in reducing pharmacokinetic variability and exposure differences between light and heavy subjects across the population. The pharmacokinetic variability introduced by either dosing regimen is moderate relative to the variability generally observed in pharmacodynamics, efficacy and safety. Therefore, mAb dosing can be flexible. Given many practical advantages, fixed dosing is recommended to be the first option in first-in-human studies with mAbs. The dosing strategy in later stages of clinical development could then be determined based on combined knowledge of the body weight effect on pharmacokinetics, safety and efficacy from the early clinical trials.

Introduction

The aim of a dosing strategy for therapeutics is to optimize the therapeutic outcome by minimizing adverse effects and maximizing efficacy across the target patient population. Multiple factors including pharmacokinetics, pharmacodynamics, exposure-response (efficacy/safety) relationships, disease burden, patient characteristics, compliance and pharmacoeconomics

affect the decision on the clinical dose and dose regimen.[1,2] An important consideration here is whether patients should be dosed based on body size, or whether body size-independent (fixed) dosing offers a viable alternative. A review of approved therapeutic monoclonal antibodies (mAbs) does not indicate a clear rationale for determining the dosing strategy. Body size-based dosing (i.e. a dose proportional to the body size) is being used more often for mAbs, with the perception that this dosing approach results in reduction of inter-subject variability in drug exposure, and controlling for this pharmacokinetic variability in turn significantly reduces variability in the response to drug treatment across the population.[3,4] As shown in table I, more than half of the currently marketed mAbs are dosed based on body size.

The use of body size-based dosing likely arose from the extrapolation of the starting dose in the first-in-human (FIH) study from doses used in preclinical experiments in animals.[3,29] However, a rigorous scientific rationale for body size-based dosing of mAbs in adults is lacking. Although a strong and even proportional relationship of body size to the volume of distribution and drug metabolizing capacity is usually demonstrated across species from mice to humans,[30] it is not necessarily the case within the human adult population, with a body size range of only 2- to 3-fold. Body size-based dosing can be justified through the observation of a statistically significant body size effect on pharmacokinetic parameter(s) in the population pharmacokinetic analysis; however, even in these cases, dosing by body weight may over-adjust for the body size effect as the pharmacokinetics are rarely proportional to body size.

mAbs reveal many unique pharmacokinetic/pharmacodynamic characteristics that differ from those of therapeutic small molecules and the dosing paradigm for mAbs needs to be assessed in the context of these characteristics. Typically, the pharmacokinetic variability of mAbs is small (30 50%) relative to the pharmacodynamic variability[1] and a small reduction in pharmacokinetic variability may not improve consistency in the therapeutic outcome of mAbs.

Most mAbs are target specific with limited off-target toxicity, hence the therapeutic window is relatively large compared with those of small molecules.[31] In general, mAbs are eliminated by a nonspecific IgG elimination pathway and a target-mediated drug disposition pathway.[1,32] The neonatal Fc receptor (FcRn) plays an important role in the nonspecific elimination pathway, while the binding affinity of a mAb to the target and the extent of the target expression are significant factors in the target-mediated pathway. Because of its *in vivo* properties, the pharmacokinetics of a mAb can be affected by multiple potential covariates including target antigen expression levels, serum protein levels and disease status, in addition to patient demographics such as age, body size and sex.[1] Consequently, body size may only explain a small portion of the overall inter-individual variability (IIV) of pharmacokinetic parameters of mAbs.[33] Therefore, the large therapeutic window and the relatively small contribution of body size to the variability in pharmacokinetics and therapeutic outcome may offer more flexibility in the mAb dosing strategy.

As a fixed dosing regimen would administer the same amount of drug to a patient regardless of the patient s body size, it offers advantages of convenience, compliance, cost effectiveness and safety due to less risk of dosing errors. Therefore, it is important to consider fixed dosing as an alternative to body size-based dosing at the time a drug is ready to move into clinical development. The dosing strategy for oncology mAbs has been evaluated and discussed in several publications.[4,34,35] Recently, a comparison of fixed dosing and body size-based dosing was conducted for 12 marketed mAbs, using published pharmacokinetic/pharmacodynamic models.[36] Results showed that the two dosing approaches performed similarly in terms of pharmacokinetic and/or pharmacodynamic variability and may therefore justify fixed dosing for FIH studies, given its advantages in dose preparation.

Encouraged by these retrospective analyses, we wanted to systematically evaluate the impact of fixed versus body size-based dosing on drug exposure of mAbs through theoretical simulations and a case study with mAbs that are marketed or under clinical development. As body weight-based dosing has been more commonly used for mAbs, it was studied as a special case of body size-based dosing. The study intended to demonstrate how the body weight effect on the main pharmacokinetic parameters (i.e. clearance [CL] and the volume of distribution) translates into the body weight effect on exposure variability, followed by a comparison of the exposure variability with fixed and body weight-based dosing. By investigating the conditions under which either dosing regimen would provide for less overall IIV in various pharmacokinetic exposure metrics, this study aims to provide insights to guide the selection of the clinical dosing strategy for mAbs in the human adult population.

Methods

Assessment of Body Weight Distribution

Body weight data were taken from the Genentech Inc. clinical trial database from 2519 adult patients with rheumatoid arthritis, breast cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer and non-Hodgkin s lymphoma. The

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Table I. Summary of population pharmacokinetic models and dosing regimens for US FDA-approved monoclonal antibodies

Trade name (generic name)	Target	Antibody type	Approval date	Therapeutic area	Dosing approach	Population pharmacokinetic model	N	Ref.
Actemra (tocilizumab)	IL-6 receptor	Humanized	2010	Immunology	mg/kg, IV	$CL\ (L/d) = 0.3 \times \left(\frac{BSA}{1.8}\right)^{0.7} \left(\frac{HDLC}{54}\right)^{-0.2} \left(\frac{LRF}{4.7}\right)^{0.1} (1 - 0.16 \times SEX) \times \exp(\eta_{CL})$ $V_1\ (L) = 3.5 \times \left(\frac{PROT}{74}\right)^{-1.1} \left(\frac{ALBU}{38}\right)^{0.7} \times \exp(\eta_{V_1})$ $V_m\ (mg/d) = 7.5 \times \left(\frac{ALBU}{38}\right)^{-0.4} \left(\frac{CL_{CR}}{106}\right)^{0.2} (1 + 0.11,\ \text{if Smoker}) \times \exp(\eta_{V_m})$	1793	5
Arzerra (ofatumumab)	CD-20	Human	2009	Oncology	mg, IV	Volume of distribution and CL increased with BW, but not clinically significant	162	6
Avastin (bevacizumab)	VEGF	Humanized	2004	Oncology	mg/kg, IV	$CL\ (L/d) = 0.207 \times \left(\frac{BW}{74}\right)^{0.368} \left(\frac{ALBU}{37}\right)^{-0.726} \left(\frac{ALKP}{102}\right)^{0.133} \left(\frac{AST}{26}\right)^{0.0715}$ $\times (1 + 0.264 \times SEX)(CHEMEF) \times \exp(\eta_{CL})$ $V_1\ (L) = 2.66 \times \left(\frac{BW}{74}\right)^{0.411} \left(\frac{ALBU}{37}\right)^{-0.333} (1 + 0.221 \times SEX) \times \exp(\eta_{V_1})$	491	7
Campath (alemtuzumab)	CD52	Humanized	2001	Oncology	mg, IV	No body size effect on CL or V_1 $V_m(\mu g/h) = 1020 \times \left(\frac{WBC}{10 \times 10^9/L}\right)^{0.194} \times \exp(\eta_{Vm})$ $Km(\mu g/L) = 338 \times \exp(\eta_{Km})$ $V_1(L) = 11.3 \times \exp(\eta_{V1})$	67	8
Erbitux (cetuximab)	EGFR	Chimeric	2004	Oncology	mg/m^2, IV	$V_m\ (mg/h) = 4.38 \times [1 + 0.0108 \times (IBW - 64) + 0.0216 \times (WBC - 6.8)]$ $\times \exp(\eta_{V_m})$ $Km\ (\mu g/mL) = 74 \times \exp(\eta_{Km})$ $V_1\ (L) = 2.83 \times [1 + 0.0083 \times (BW - 60)] \times \exp(\eta_{V_1})$	143	9
Herceptin (trastuzumab)	HER2	Humanized	1998	Oncology	mg/kg, IV	$CL\ (L/d) = 0.241 \times \left(\frac{BW}{68}\right)^{0.557} \left(\frac{ALKP}{107}\right)^{0.141} \left(\frac{SHED}{17.9}\right)^{0.102} \times \exp(\eta_{CL})$ $V_1\ (L) = 3.02 \times \left(\frac{BW}{68}\right)^{0.484} \times \exp(\eta_{V_1})$	265	10
Humira (adalimumab)	TNFα	Human	2002	Immunology	mg, SC	Slight increase in CL with an increase in BW	45	11
Ilaris (canakinumab)	IL-1β	Human	2009	Immunology	mg (BW >40 kg), mg/kg (15 ≤ BW ≤ 40), SC	CL and V_{ss} varied according to BW	NA	12
Mylotarg (gemtuzumab ozogamicin)	CD33	Humanized ADC	2000	Oncology	mg/m^2, IV	No reported BW effect on CL or V_1 for both antibody and total calicheamicin	59	13

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Table I. Contd

Trade name (generic name)	Target	Antibody type	Approval date	Therapeutic area	Dosing approach	Population pharmacokinetic model	N	Ref.
Orthoclone OKT3 (muromonab-CD3)	CD3	Murine	1986	Transplantation	mg, IV	NA	NA	NA
Raptiva (efalizumab)	CD11	Humanized	2002	Immunology	mg/kg, SC	$CL/F\ (L/d) = 1.29 \times \left(\frac{BW}{91.0}\right)^{0.754} (1 + 0.0997 \times OBS) \left(\frac{PASI}{17.1}\right)^{0.220} \times \left(\frac{LYM}{1.82}\right)^{0.165} (1 - 0.24 \times Dose) \times \exp\left(\eta_{CL/F}\right)$ $V_d/F\ (L) = 9.13 \times \exp\left(\eta_{V_d/F}\right)$	1088	14
ReoPro (abciximab)	GP IIB/IIIA receptor	Chimeric Fab	1994	Cardiology	mg/kg, IV	$CL\ (L/h) = (22.0 + 0.018 \times (BW - 87)) \times \exp(\eta_{CL})$ $V_1\ (L) = 11 \times \exp(\eta_{V_1})$	152	15
Remicade (infliximab)	TNFα	Chimeric	1998	Immunology	mg/kg, IV	$CL\ (L/d) = [0.273 + (WBC - 7.9) \times 0.0106](1 + IR \times 0.419) \times \exp(\eta_{CL})$ $V_1\ (L) = 3.06 \times \left(\frac{BSA}{1.94}\right)^{0.744} (1 - SEX \times 0.1) \times \exp(\eta_{V_1})$	274	16
Rituxan (rituximab)	CD20	Chimeric	1997	Oncology and immunology	mg/m^2 or mg, IV, SC	NHL: $CL\ (mL/d) = 585 \times \exp(-0.0459 \times TIME) \times \exp(\eta_{CLNL}) + 138 \times \exp(\eta_{CLL})$ $V_1\ (mL) = 2700 \times \left(\frac{BSA}{1.9}\right)^{1.26} \times \exp(\eta_{V_1})$	298	NP
						RA: $CL\ (mL/d) = 335 \times \left(\frac{BW}{73.6}\right)^{0.470} \left(\frac{AGE}{53}\right)^{-0.249} \left(\frac{RF}{109}\right)^{0.0961} \left(\frac{CRP}{16}\right)^{0.0863} \times \left(\frac{ALBU}{38}\right)^{-1.08} \times (1 + SEX \times 0.202) \times \exp(\eta_{CL})$ $V_1\ (mL) = 3140 \times \left(\frac{BW}{73.6}\right)^{0.379} \left(\frac{CRP}{16}\right)^{0.0199} (1 + SEX \times 0.173) \times \exp(\eta_{V_1})$	2005	NP
Simponi (golimumab)	TNFα	Human	2009	Immunology	mg, SC	PsA: $CL/F\ (L/d) = 1.38 \times \left(\frac{BW}{70}\right)^{0.778} \left(\frac{CRP}{0.6}\right)^{0.0575} \times 1.1^{IRP} \times 1.13^{SMOK} \times \exp\left(\eta_{CL/F}\right)$ $V_d/F\ (L) = 24.9 \times \left(\frac{BW}{70}\right)^{0.805} \times \exp\left(\eta_{V_d/F}\right)$	337	17
						RA: $CL\ (L/d) = 0.40 \times \exp(\eta_{CL})$ $V_1\ (L) = 3.07 \times \left(\frac{BW}{72.3}\right)^{0.86} \times \exp(\eta_{V_1})$	21	18
Simulect (basiliximab)	IL-2 receptor (CD25)	Chimeric	1998	Transplantation	mg, IV	No significant BW effect on CL or V_1	184	19

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Table I. Contd

Trade name (generic name)	Target	Antibody type	Approval date	Therapeutic area	Dosing approach	Population pharmacokinetic model	N	Ref.
Soliris (eculizumab)	Complement protein C5	Humanized	2007	Immunology	mg, IV	No significant BW effect on CL or V_1 reported	40	20
Stelara (ustekinumab)	IL-12/23p40	Human	2005	Immunology	BW-stratified, SC	$CL/F\ (L/d) = 0.465 \times \left(\frac{BW}{90}\right)^{0.84} (1 + 0.287 \times DIAB)(1 + 0.355 \times IRP) \times \left(\frac{ALBU}{34.5}\right)^{-0.896} \left(\frac{CL_{CR}}{120}\right)^{0.188} (1 + 0.059 \times SEX) \left(\frac{ALKP}{80}\right)^{0.113} \times \exp(\eta_{CL})$ $V_d/F\ (L) = 15.7 \times \left(\frac{BW}{90}\right)^{0.807} (1 - 0.111 \times RGP)(1 + 0.132 \times DIAB) \times \exp(\eta_{V_d/F})$	1937	21
Synagis (palivizumab)	RSV F protein	Humanized	1998	Virology	mg/kg, IM	Unknown	NA	22
Tysabri (natalizumab)	α4β1 integrin	Humanized	2006	Immunology	mg, IV	CL weakly correlated with BW	NA	23
Vectibix (panitumumab)	EGFR	Human	2006	Oncology	mg/kg, IV	$CL\ (L/d) = 0.273 \times \left(\frac{BW}{80}\right)^{0.411} \times 0.769^{SEX} \times 0.861^{LUNG} \times 0.957^{RENAL} \times 0.870^{OTHER} \times \exp(\eta_{CL})$ $V_1\ (L) = 3.95 \times \left(\frac{BW}{80}\right)^{0.526} \times 0.769^{SEX} \times \exp(\eta_{V_1})$ $V_m\ (mg/d) = 12.1 \times \left(\frac{BW}{80}\right)^{0.621} \times \left(\frac{AGE}{60}\right)^{-0.495} \times \exp(\eta_{V_m})$ $Km\ (\mu g/mL) = 0.426 \times \exp(\eta_{Km})$	1200	24
Xolair[a] (omalizumab)	IgE	Humanized	2003	Immunology	IgE levels and BW-stratified, SC	PKPD model $CL/F\ (mL/h) = 7.32 \times \left(\frac{BW}{61.1}\right)^{0.911} \times \exp(\eta_{CL})$ $V_d/F\ (mL) = 5900 \times \left(\frac{BW}{61.1}\right)^{0.658} \times \exp(\eta_{V_d/F})$	202	25
Zenapax[b] (daclizumab)	IL-2 receptor (CD25)	Humanized	1997	Transplantation	mg/kg, IV	$CL\ (L/h) = 0.0118 \pm 0.0007 \times \left(\frac{BW}{75}\right)^{0.463 \pm 0.192}$ $V_1\ (L) = 2.39 \pm 0.134$	16	26

a Fixed dosing is used in clinical development for the indication of chronic rhinosinusitis.[27]

b Fixed dosing is used in clinical development for the indication of multiple sclerosis.[28]

ADC = antibody-drug conjugate; **ALBU** = serum albumin concentration; **ALKP** = serum alkaline phosphatase concentration; **AST** = aspartate aminotransferase (also named as SGOT [serum glutamic oxaloacetic transferase]); **BSA** = body surface area; **BW** = bodyweight; **CHEMEF** = combined chemotherapy effect; **CL** = clearance; **CL_{CR}** = creatinine clearance; **CL/F** = clearance after subcutaneous administration; **CLL** = linear clearance; **CLNL** = nonlinear clearance; **CRP** = C-reactive protein; **DIAB** = diabetes comorbidity; **EGFR** = epidermal growth factor receptor; **GP** = glycoprotein; **HDLC** = high-density lipoprotein cholesterol; **HER2** = human EGFR2; **IBW** = ideal body weight; **IL** = interleukin; **IM** = intramuscular; **IR** = antibody-to-infliximab status; **IRP** = positive immune response to monoclonal antibody; **IV** = intravenous; **Km** = Michaelis-Menten constant; **LRF** = logarithm of rheumatoid factor; **LYM** = baseline lymphocyte count; **NA** = not available; **NHL** = non-Hodgkin's lymphoma; **NP** = not published; **OBS** = indicator for obese or not obese; **PASI** = Psoriasis Area and Severity Index; **PKPD** = pharmacokinetic/pharmacodynamic; **PROT** = total protein; **PsA** = psoriatic arthritis; **RA** = rheumatoid arthritis; **Ref.** = reference; **RF** = rheumatoid factor; **RGP** = race group; **RSV** = respiratory syncytial virus; **SC** = subcutaneous; **SHED** = HER2 shed antigen level; **SMOK** = smoking status; **TNF** = tumour necrosis factor; **V_1** = central volume of distribution; **V_d/F** = volume of distribution after subcutaneous administration; **VEGF** = vascular endothelial growth factor; **V_m** = maximum elimination rate; **V_{ss}** = steady-state volume of distribution; **WBC** = white blood cell count.

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observed body weight ranged from 29 to 195 kg. The data suggest a log-normal distribution[37] with a mean (standard deviation), median, and 10th and 90th percentiles of 74 (22), 78, 56 and 112 kg, respectively. Based on this body weight distribution pattern, body weight data from 1000 subjects were simulated to evaluate the body weight effect on exposure following fixed dosing or body weight-based dosing of mAbs. Figure 1 displays the simulated body weight data overlaid with the actual body weight data described above.

Population Pharmacokinetic Model

Typically for mAbs, a generic two-compartment first-order elimination model was used for simulation. To simplify the simulation, only body weight was built into the model as a covariate on CL and the central volume of distribution (V_1). The effects of body weight on CL and V_1 were described using the power model as shown below (equation 1):

$$CL_i = \theta_1 \bullet \left(\frac{BW_i(kg)}{78}\right)^{\theta_{BW_CL}} \bullet \exp\left(\eta_{CL_i}\right)$$
$$V_1 i = \theta_2 \bullet \left(\frac{BW_i(kg)}{78}\right)^{\theta_{BW_V_1}} \bullet \exp\left(\eta_{V_1 i}\right)$$
$$Q = \theta_3$$
$$V_2 = \theta_4 \qquad \text{(Eq. 1)}$$

where CL_i and V_{1i} are the estimated CL and V_1 values, respectively, for individual i; θ_1 and θ_2 are the typical population values (geometric means) of CL and V_1, respectively; BW_i is the body weight of individual i; 78 is the median body weight of the simulated population; θ_{BW_CL} and θ_{BW_V1} represent the exponential functions of the body weight effects on CL and V_1, respectively; η_{CLi} and η_{V1i} are the inter-individual random effects on CL and V_1, respectively, for individual i, and are assumed to be normally distributed with a mean of 0 and variance of ω^2 [$\eta \sim N(0, \omega^2)$]; Q is intercompartmental clearance; and V_2 is the peripheral volume of distribution.

No body weight effect was tested on Q and V_2. A full error model (i.e. additive and proportional) was used to describe the residual variability, where both the additive and proportional residual errors were assumed to be normally distributed (equation 2):

$$C_{ij} = \hat{C}_{ij} * (1 + \varepsilon_{1_{ij}}) + \varepsilon_2 ij \qquad \text{(Eq. 2)}$$

where C_{ij} is the jth model-predicted value in individual i; and ε_{1ij} and ε_{2ij} are proportional and additive residual random errors, respectively, for individual i and measurement j, and are each assumed to be independently and identically distributed following a normal distribution with a mean of 0 and variance of σ^2 [$\varepsilon \sim N(0, \sigma^2)$].

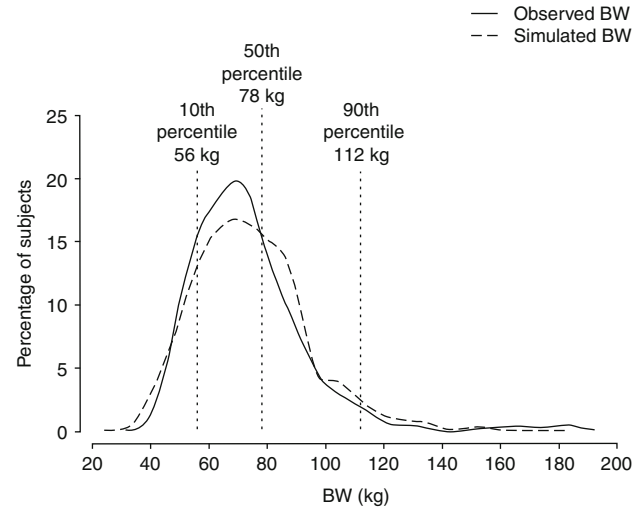

Fig. 1. Body weight (BW) distribution: BW distribution data (solid line) were collected in Genentech clinical trials from 2519 adult patients with rheumatoid arthritis, breast cancer, colorectal cancer, non-small cell lung cancer, ovarian cancer and non-Hodgkin's lymphoma. The dashed line indicates the simulated BW data for 1000 subjects. The simulated subjects are grouped, based on BW, into one of three subpopulations: normal (BW between 10th and 90th percentiles), light (BW ≤10th percentile) and heavy (BW ≥90th percentile).

Simulation Method

Typical pharmacokinetic parameter values for therapeutic IgG1 mAbs[1] were used in each simulation: CL = 0.211 L/day, V_1 = 2.92 L, Q = 0.398 L/day and V_2 = 2.87 L. These estimates were based on a published bevacizumab population pharmacokinetic model[7] with slight modification using an updated dataset from 524 patients. To simulate different scenarios of the body weight effect on pharmacokinetics, the exponents of the body weight effects on CL (θ_{BW_CL}) and V_1 (θ_{BW_V1}) were varied from 0 to 1 in increments of 0.1, where 0 indicates no effect and 1 indicates a linear effect of body weight on CL or V_1. This resulted in 121 simulation scenarios of the body weight effect on CL and V_1.

A fixed dose of 1000 mg or a body weight-based dose of 15 mg/kg (i.e. a total dose of 1170 mg for a median body weight subject) administered intravenously once every 3 weeks (q3wk) was simulated. Since linear kinetics were assumed in the simulations, a small discrepancy in the total dose administered was not expected to impact the simulation results. Simulations were performed using first-order conditional estimation with interaction (FOCEI) with NONMEM VI 1.1 software (Globomax LLC, Hanover, MD, USA).

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Three exposure metrics were considered as potential pharmacokinetic drivers for therapeutic efficacy and safety and therefore were evaluated under different dosing assumptions: the steady-state peak serum concentration ($C_{max,ss}$), steady-state trough serum concentration ($C_{min,ss}$) and steady-state area under the serum concentration-time curve (AUC_{ss}). The data were obtained after six q3wk doses, which approximates steady state. AUC_{ss} was calculated using the trapezoidal rule[38] based on the simulated concentration-time data.

Individual Simulations

To demonstrate the body weight effect on exposure with fixed dosing and body weight-based dosing of mAbs, pharmacokinetic profiles of three individual subjects with low body weight (10th percentile: 56 kg), median body weight (78 kg) and high body weight (90th percentile: 112 kg) were simulated. IIV on CL, V_1, Q and V_2, and residual errors were set to 0 for the simulation of each individual subject, in order to only evaluate the body weight effect. Using the median body weight subject as the reference, the fractional change of the simulated exposure measures as a function of θ_{BW_CL} and θ_{BW_V1} was calculated for the light (body weight = 56 kg) and heavy (body weight = 112 kg) subjects.

Population Simulations

To compare exposure variability between fixed dosing and body weight-based dosing in a population, Monte-Carlo simulations were performed in 1000 simulated subjects per scenario with a body weight distribution derived from the existing body weight database described earlier. For each scenario, 1000 subjects were grouped into three subpopulations based on their body weight distributions: normal (body weight between 10th and 90th percentiles), light (body weight ≤10th percentile), and heavy (body weight ≥90th percentile).

The population simulation applied 30% IIV (for CL and V_1), 30% proportional residual error, and 0.1 μg/mL additive error, which are realistic assumptions of the random effect on mAb pharmacokinetics.[1]

To quantify the exposure variability as a result of fixed and body weight-based dosing regimens, the 90% range (i.e. between the 5th and 95th percentiles) of the simulated exposure of all subjects was calculated using the following equation for AUC_{ss} (equation 3):

$$90\%\ \text{Range} = \frac{AUC_{ss}(95\text{th}) - AUC_{ss}(5\text{th})}{AUC_{ss}(\text{median of normal})} \times 100\% \quad \text{(Eq. 3)}$$

where AUC_{ss}(95th) and AUC_{ss}(5th) are the 95th and 5th percentiles, respectively, of the simulated AUC_{ss} in all subjects; and AUC_{ss}(median of normal) is the median simulated AUC_{ss} in the normal subpopulation. Similar calculations were also performed for $C_{min,ss}$ and $C_{max,ss}$. The difference between fixed and body weight-based dosing in the 90% range of simulated exposure was then calculated as (equation 4):

$$\text{Difference} = 90\%\ \text{Range (fixed)} - 90\%\ \text{Range (BW-based)} \quad \text{(Eq. 4)}$$

To quantify the deviation of exposure for extreme body weight subjects from the normal body weight subjects, the percentage deviation in the median exposure of the light or heavy subpopulation relative to the normal subpopulation was calculated using the following equation (equation 5) for AUC_{ss}:

$$\%\text{deviation} = \frac{AUC_{ss}(\text{median of extreme}) - AUC_{ss}(\text{median of normal})}{AUC_{ss}(\text{median of normal})} \times 100\% \quad \text{(Eq. 5)}$$

where extreme refers either to the light or heavy subpopulation. The same calculation was also conducted for $C_{min,ss}$ and $C_{max,ss}$.

Case Study with Therapeutic Monoclonal Antibodies that Are Marketed or in Development

In the theoretical simulations described above, a generic population pharmacokinetic model was used with body weight as the only covariate, as mentioned earlier. To evaluate the results from the theoretical simulations, the actual population pharmacokinetic models from three marketed products (i.e. bevacizumab, trastuzumab and rituximab) and five molecules (GNE1, GNE2, GNE3, GNE4 and GNE5) under Genentech development were chosen. Although their base models are similar (i.e. a two-compartment linear model), the final models contain different demographic and pathophysiological covariates depending on observed behaviour for each mAb. The detailed model structures are listed in tables I and II. Simulations were performed using the actual population pharmacokinetic models for these marketed and development mAbs. The difference in the 90% range of exposure (AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$) between fixed dosing and body weight-based dosing obtained for the actual simulations was compared with the results obtained from the generic population pharmacokinetic model at given θ_{BW_CL} and θ_{BW_V1} values for each molecule. A visual comparison between these two sets of results was performed to evaluate the predictive performance of generic population pharmacokinetic simulation of IIV by fixed dosing versus body weight-based dosing.

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Table II. Summary of population pharmacokinetic models and dosing regimens for monoclonal antibodies in development at Genentech

Name	Antibody type	Therapeutic area	Dosing approach	Population pharmacokinetic model	N	Ref.
GNE1	Humanized	Oncology	mg/kg, IV	$CL\ (L/d) = 0.677 \times \left(\frac{BW}{71.4}\right)^{0.882} \times \exp(\eta_{CL})$ $V_1\ (L) = 4.15 \times \left(\frac{BW}{76.8}\right)^{0.872} \times \exp(\eta_{V_1})$	34	NP
GNE2	Human	Oncology	mg, IV	$CL\ (L/d) = 0.230 \times \left(\frac{BW}{70.7}\right)^{0.549} \left(\frac{ALBU}{39}\right)^{-1.13} \left(\frac{ALKP}{104}\right)^{0.137} \times (TUMOR \times 1.29) \bullet \exp(\eta_{CL})$ $V_1\ (L) = 2.66 \times \left(\frac{BW}{70.7}\right)^{0.498} (1.11)^{SEX} \bullet \exp(\eta_{V_1})$	300	39
GNE3	Humanized	Immunology	mg, IV, SC	$CL\ (L/d) = 0.222 \times \left(\frac{BW}{81.6}\right)^{0.949} \times \exp(\eta_{CL})$ $V_1\ (L) = 2.68 \times \left(\frac{BW}{81.6}\right)^{0.583} \times \exp(\eta_{V_1})$	48	NP
GNE4	Humanized	Oncology	mg/kg, IV	$CL\ (L/d) = 0.425 \times \left(\frac{BW}{76}\right)^{0.534} \times \exp(\eta_{CL})$ $V_1\ (L) = 3.36 \times \left(\frac{BW}{76}\right)^{0.534} \times 0.792^{STUDY} \times \exp(\eta_{V_1})$	126	NP
GNE5	Human	Oncology	mg/kg, IV	$CL\ (L/d) = 0.443 \times 0.638^{(STUDY\ -\ 1)} \times \exp(\eta_{CL})$ $V_1\ (L) = 3.87 \times \left(\frac{BW}{77}\right)^{0.257} \times 0.16^{(SEX\ -\ 1)} \times \exp(\eta_{V_1})$	165	NP
GNE6	Humanized	Immunology	mg, SC	No significant BW effect on CL or V_1	41	NP
GNE7	Humanized	Oncology	mg/kg, SC	$CL\ (L/d) = 0.313 \times \exp(\eta_{CL})$ $V_1\ (L) = 3.68 \times \left(\frac{BW}{75.2}\right)^{0.506} \times \exp(\eta_{V_1})$	60	NP
GNE8	Humanized	Immunology	mg, SC	$k_a\ (day^{-1}) = 0.17 \times \exp(\eta_{k_a})$ $CL\ (mL/d) = 182 \times \left(\frac{BW}{79}\right)^{0.683} \times \exp(\eta_{CL})$ $V_2\ (mL) = 3470 \times \left(\frac{BW}{79}\right)^{0.489} \times \exp(\eta_{V_2})$	59	NP
GNE9	ADC	Oncology	IV	$CL\ (L/h) = 0.0293 \times \left(\frac{BW}{70}\right)^{0.423} \left(\frac{ALBU}{40}\right)^{-0.450} \left(\frac{TMBD}{8}\right)^{0.0806} \times \left(\frac{AST}{31}\right)^{0.0908} \times \exp(\eta_{CL})$ $V_1\ (L) = 3.30 \times \left(\frac{BW}{70}\right)^{0.524} \times \exp(\eta_{V_1})$	275	40

ADC = antibody drug conjugate; **ALBU** = serum albumin concentration; **ALKP** = serum alkaline phosphatase concentration; **AST** = serum aspartate aminotransferase; **BW** = body weight; **CL** = clearance; **IV** = intravenous; $\mathbf{k_a}$ = absorption rate constant; **NP** = not published; **Ref.** = reference; **SC** = subcutaneous; **TMBD** = tumour burden; $\mathbf{V_1}$ = central volume of distribution; $\mathbf{V_2}$ = peripheral volume of distribution.

Subsequently, body weight exponents θ_{BW_CL} and θ_{BW_V1} were obtained from published population pharmacokinetic models for a total of ten marketed mAbs (basiliximab, bevacizumab, daclizumab, efalizumab, golimumab, omalizumab, panitumumab, rituximab, trastuzumab and ustekinumab) and nine mAbs (i.e. GNE1, GNE2, GNE3, GNE4, GNE5, GNE6, GNE7, GNE8 and GNE9) in clinical development. These values were then mapped onto the theoretical simulation plots.

Results

Effect of Fixed and Body Weight-Based Dosing on Individual Exposure in Heavy or Light Subjects

An important consideration for dosing strategy selection is to reduce the deviation in exposure of heavy and light subjects from that of the normal body weight subjects. To assess the impact of fixed versus body weight-based dosing on exposure,

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the individual pharmacokinetic exposure (AUC_{ss}, $C_{min,ss}$ and $C_{max,ss}$) of a typical mAb in subjects with median, heavy (90th percentile) and light (10th percentile) body weight was simulated as a function of θ_{BW_CL} and θ_{BW_V1}.

The simulation results are shown in figure 2. As illustrated by the horizontal planes in the 3D plots, AUC_{ss}, $C_{min,ss}$ and $C_{max,ss}$ values for a median body weight subject did not change with θ_{BW_CL} and θ_{BW_V1} when the mAb was given with either fixed or body weight-based dosing.

Following fixed dosing (figure 2a, 2c and 2e), the same exposure values are expected for median and extreme body weight subjects when there is no body weight effect on CL and V_1 (i.e. $\theta_{BW_CL}=0$ and $\theta_{BW_V1}=0$). As θ_{BW_CL} and θ_{BW_V1} values increase from 0 to 1, exposure decreases in the heavy subject and increases in the light subject, suggesting the heavy subject is underexposed whereas the light subject is overexposed as compared with the median body weight subject.

In contrast, following body weight-based dosing (figure 2b, 2d and 2f), the extreme body weight subjects have the same exposure as the median body weight subject when both θ_{BW_CL} and θ_{BW_V1} are 1; as the exponents decrease from 1 to 0, the light subject tends to be underexposed and the heavy subject tends to be overexposed, compared with the median body weight subject.

Also as illustrated in figure 2, the body weight effect on CL, but not on V_1, is the main driver of differences in AUC_{ss} and $C_{min,ss}$, whereas both θ_{BW_CL} and θ_{BW_V1} affect $C_{max,ss}$ to a similar extent. When θ_{BW_CL} and θ_{BW_V1} vary between 0 and 1, the percentage change of exposure for the light or heavy subject from the median body weight subject is within ±50% for all three exposure variables following both fixed and body weight-based dosing.

Comparison of Inter-Individual Variability (IIV) in Exposure between Fixed and Body Weight-Based Dosing

The individual simulations provide insights into the effect of the dosing regimen on mean exposure in heavy and light subjects, but do not account for the IIV in pharmacokinetic parameters and body weight distribution in a given patient

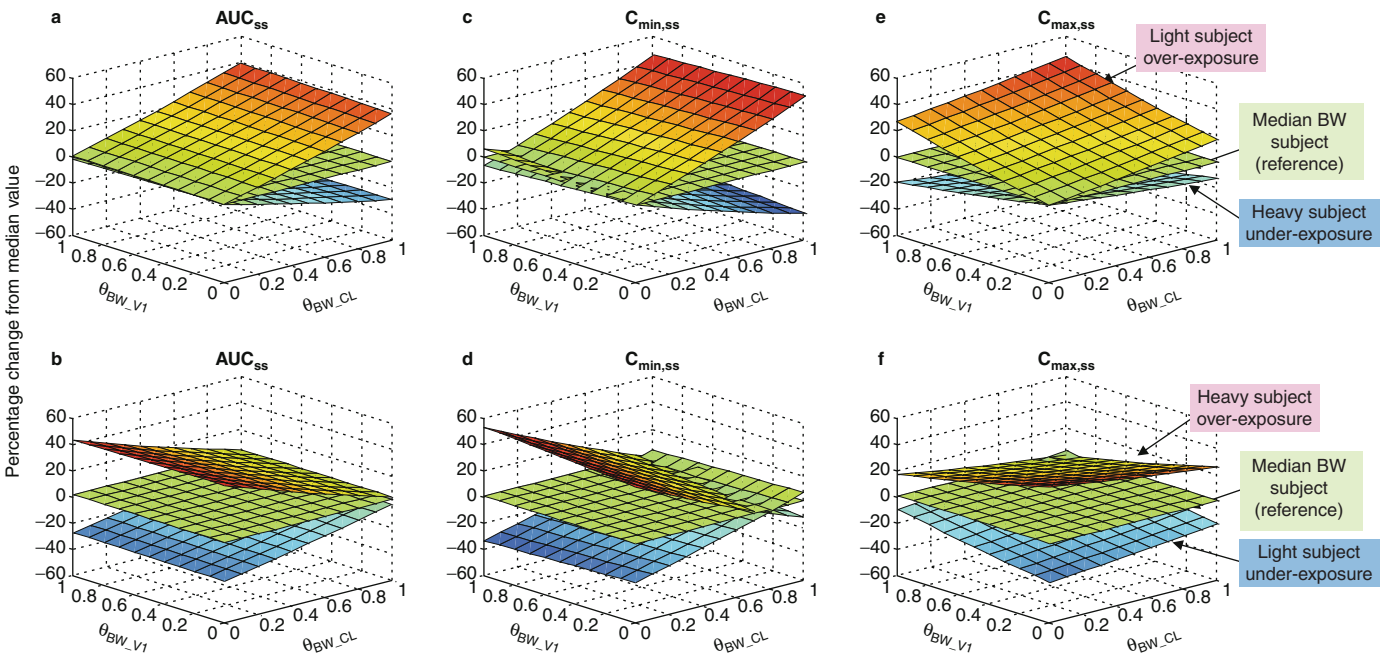

Fig. 2. Change of exposure as a function of body weight (BW) effects on clearance (θ_{BW_CL}) and the central volume of distribution (θ_{BW_V1}): percentage changes of (**a** and **b**) the steady-state area under the serum concentration time curve (AUC_{ss}), (**c** and **d**) the steady-state trough serum concentration ($C_{min,ss}$) and (**e** and **f**) the steady-state peak serum concentration ($C_{max,ss}$) as a function of θ_{BW_CL} and θ_{BW_V1} for a light or heavy subject compared with a median BW subject are plotted, following (**a**, **c** and **e**) a fixed dose of 1000 mg or (**b**, **d** and **f**) a BW-based dose of 15 mg/kg. The middle green data series in all graphs represents exposure for the median BW subject, which does not change with the change of θ_{BW_CL} and θ_{BW_V1}. In (**a**, **c** and **e**), the upper and lower data series show over-exposure for the light subject (10th percentile: 56 kg) and under-exposure for the heavy subject (10th percentile: 112 kg), respectively, given the fixed dose. In (**b**, **d** and **f**), the upper and lower data series show over-exposure for the heavy subject and under-exposure for the light subject, respectively, given the BW-based dose.

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population. Hence, population pharmacokinetic simulations were performed as described in the Methods section. The difference in the simulated 90% range (i.e. from the 5th to the 95th percentiles) of exposure in all subjects between the two dosing regimens was calculated across all possible combinations of θ_{BW_CL} and θ_{BW_V1}. This is used as a metric to evaluate the exposure variability with fixed versus body weight-based dosing.

Figure 3 shows the difference in exposure variability (i.e. the 90% range of AUC_{ss}, $C_{min,ss}$ and $C_{max,ss}$) as the function of θ_{BW_CL} and θ_{BW_V1} between fixed and body weight-based dosing. In figure 3a, all lines are roughly vertical, indicating that AUC_{ss} variability was affected by the body weight effect on CL but not on V_1. Compared with body weight-based dosing, fixed dosing results in less variability in AUC_{ss} when θ_{BW_CL} <0.5, similar variability when θ_{BW_CL} = 0.5 and greater variability when θ_{BW_CL} >0.5. The maximum difference in the simulated 90% range for AUC_{ss} between fixed and body weight-based dosing is ±40%.

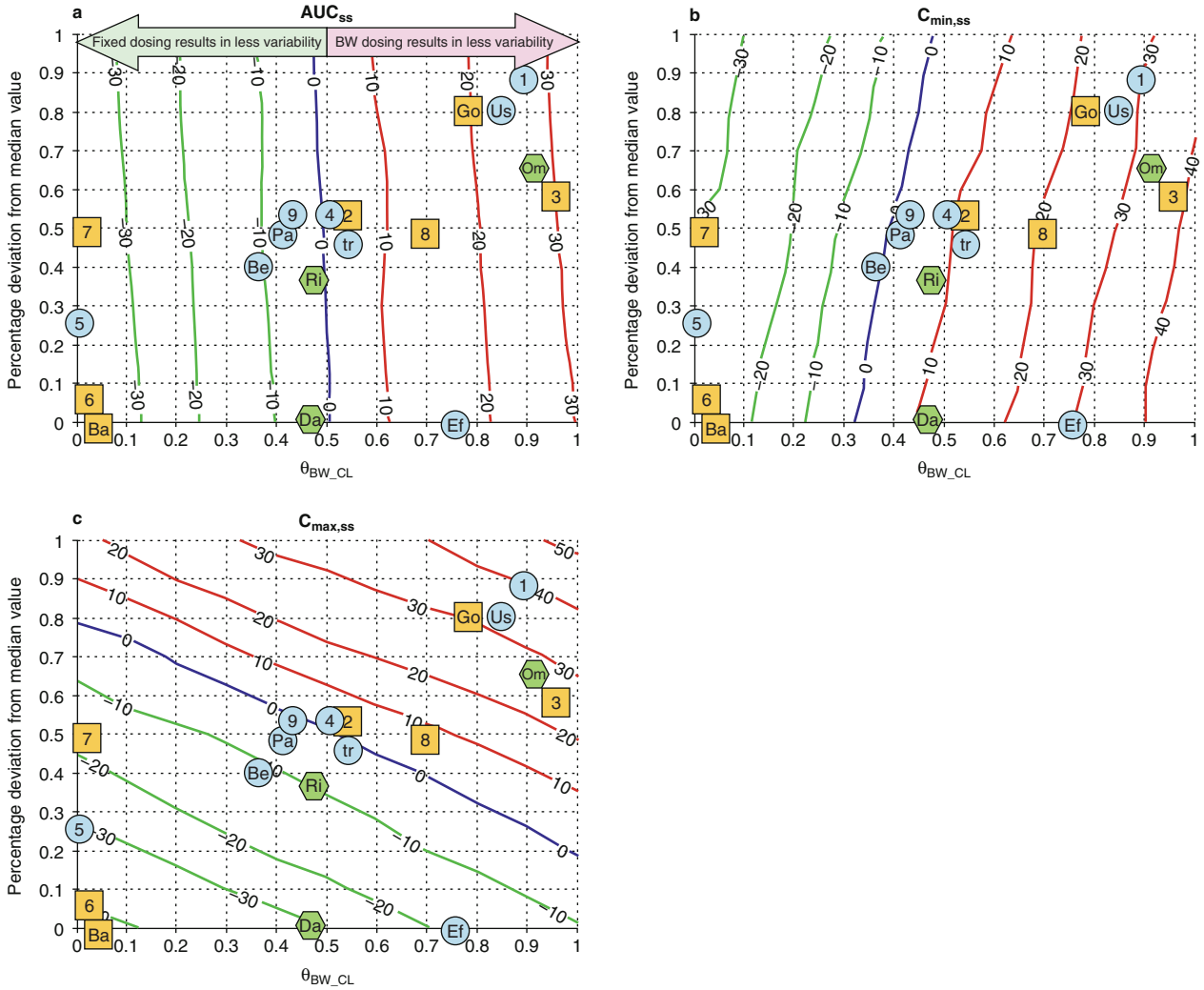

Fig. 3. Comparison of exposure variability between fixed and body weight (BW)-based dosing: the difference of the 90% range (from the 5th to the 95th percentiles) of exposure in the overall population is plotted for (**a**) the steady-state area under the serum concentration-time curve (AUC_{ss}), (**b**) the steady-state trough serum concentration ($C_{min,ss}$) and (**c**) the steady-state peak serum concentration ($C_{max,ss}$). The middle blue line labelled '0' indicates scenarios where fixed dosing and BW-based dosing have equal variability; green lines labelled with negative values indicate that fixed dosing has less variability by 10%, 20%, 30%, etc.; red lines labelled with positive values indicate that fixed dosing has more variability than BW-based dosing by 10%, 20%, 30%, etc. The BW effects on clearance (θ_{BW_CL}) and the central volume of distribution (θ_{BW_V1}) were obtained from publications (see table I) or from unpublished Genentech internal population analyses (see table II) and are mapped on the generic model simulation plots. Circles, squares and hexagons represents monoclonal antibodies administered using BW-based dosing (or BW-stratified dosing), fixed dosing, or different dosing regimens in different indications, respectively. Marketed mAbs are indicated by two initial letters, as follows: **Ba** = basiliximab; **Be** = bevacizumab; **Da** = daclizumab; **Ef** = efalizumab; **Go** = golimumab; **Om** = omalizumab; **Pa** = panitumumab; **Ri** = rituximab; **Tr** = trastuzumab; **Us** = ustekinumab. GNE molecules are indicated as numbers.

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Variability in $C_{min,ss}$ is mainly driven by the body weight effect on CL and, to a lesser extent, on V_1 (figure 3b). Both dosing regimens result in similar variability in $C_{min,ss}$ when the (θ_{BW_CL}, θ_{BW_V1}) pair falls on the line linked by a starting point of (~0.3, 0) and an end point of (~0.5, 1). On the left side of this line, fixed dosing is superior in reducing variability whereas on the right side, body weight-based dosing is superior. The maximum difference in the simulated 90% range for $C_{min,ss}$ between fixed and body weight-based dosing is ±50%.

The body weight effects on both CL and V_1 affect the variability in $C_{max,ss}$ (figure 3c). Both dosing regimens result in similar variability in $C_{max,ss}$ when the (θ_{BW_CL}, θ_{BW_V1}) pair falls on the blue line linking (0, ~0.8) and (1, ~0.2). Below this line, fixed dosing is superior to body weight-based dosing in reducing variability. As θ_{BW_CL} and θ_{BW_V1} increase, body weight-based dosing becomes more advantageous over fixed dosing in reducing the variability. As with $C_{min,ss}$, the maximum difference in the simulated 90% range for $C_{max,ss}$ between fixed and body weight-based dosing is ±50%.

Comparison of Exposure Deviation for Light and Heavy Subpopulations between Fixed and Body Weight-Based Dosing

As demonstrated in the individual simulations, light and heavy subjects may obtain relatively more or less exposure to a drug compared with the median body weight subjects, depending on the pharmacokinetic characteristics of the compound and the type of dosing approach used. This might be acceptable for mAbs with a wide therapeutic window, but might be of concern for mAbs with a narrow therapeutic window; such mAbs warrant further analysis to determine the dose-normalization approach. In this case, special attention should be paid to the exposure of the extreme body weight subjects in determining the dosing strategy. Figure 4 shows the percentage deviations in exposure (i.e. AUC_{ss}, $C_{min,ss}$ and $C_{max,ss}$) for light and heavy subjects compared with the median values in the normal subpopulation when both θ_{BW_CL} and θ_{BW_V1} are equal to 0.1, 0.5 and 0.75.

When the body weight effects on CL and V_1 are small (e.g. $\theta_{BW_CL} = 0.1$, $\theta_{BW_V1} = 0.1$) [figure 4a], the percentage deviation is smaller with fixed dosing for all three exposure measures, suggesting that fixed dosing leads to relatively less over- or under-exposure for light or heavy subjects compared with body weight-based dosing. When there is a moderate body weight effect (e.g. $\theta_{BW_CL} = 0.5$, $\theta_{BW_V1} = 0.5$) [figure 4b], the percentage deviation is similar with fixed and body weight-based dosing. In this case, body weight-based dosing does not reduce the deviation in the light and heavy subjects compared with fixed dosing; rather, it reverses the direction of the deviations. Finally, when there is a strong body weight effect (e.g. $\theta_{BW_CL} = 0.75$, $\theta_{BW_V1} = 0.75$) [figure 4c], the percentage deviation is smaller with body weight-based dosing, suggesting that body weight-based dosing reduces the over- or under-exposure for light or heavy subjects compared with fixed dosing. Of note, our results show that the light subpopulation tends to have larger deviation than the heavy subpopulation, given the current body weight distribution data. As the body weight distribution varies from population to population, this observation may need to be verified on a case-by-case basis.

Overall, for the extreme body weight subjects when both θ_{BW_CL} and θ_{BW_V1} are equal to 1, the maximum percentage deviation is within ±60% for AUC_{ss} and $C_{max,ss}$ and within 80% for $C_{min,ss}$ for either fixed or body weight-based dosing (data not shown). Further, the scenarios (i.e. θ_{BW_CL} and θ_{BW_V1} pairs) under which fixed dosing is superior to body weight-based dosing for reducing the deviation in the extreme body weight subjects are generally consistent with those for reducing the overall IIV of exposure illustrated in figure 3.

Case Study

As described in the Methods section, the simulation results above were generated using a generic population pharmacokinetic model in which body weight is the only covariate. To evaluate the simulation method, a total of eight mAbs were chosen and independent simulations were performed using their actual population pharmacokinetic models (displayed in tables I and II). The results from the two simulation approaches (i.e. generic versus molecule-specific models) are highly correlated and randomly distributed around the unity line (figure 5), confirming that the generic model simulation is a reliable approach in assessing the fixed versus body weight-based dosing regimens.

To allow for a comparison of the simulations with reported pharmacokinetic data, θ_{BW_CL} and θ_{BW_V1} obtained from the existing population pharmacokinetic models for 19 mAbs (highlighted in tables I and II) were mapped on the theoretical simulation plots to project the difference in the IIV between fixed and body weight-based dosing. As shown in figure 3, most of the mAbs have little effect or a moderate body weight effect with θ_{BW_CL} and θ_{BW_V1} <5 or ~0.5. Consequently, these mAbs are predicted to have no significant clinical benefit from body weight-based dosing as it results in

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a minimal change (i.e. less than 20%) of variability in most exposure measures compared with fixed dosing. Only a few mAbs (golimumab, omalizumab, ustekinumab, GNE1 and GNE3) have strong body weight effects with exponents greater than 0.75, for which body weight-based dosing can lead to 20 40% reduction of variability in all exposure measures.

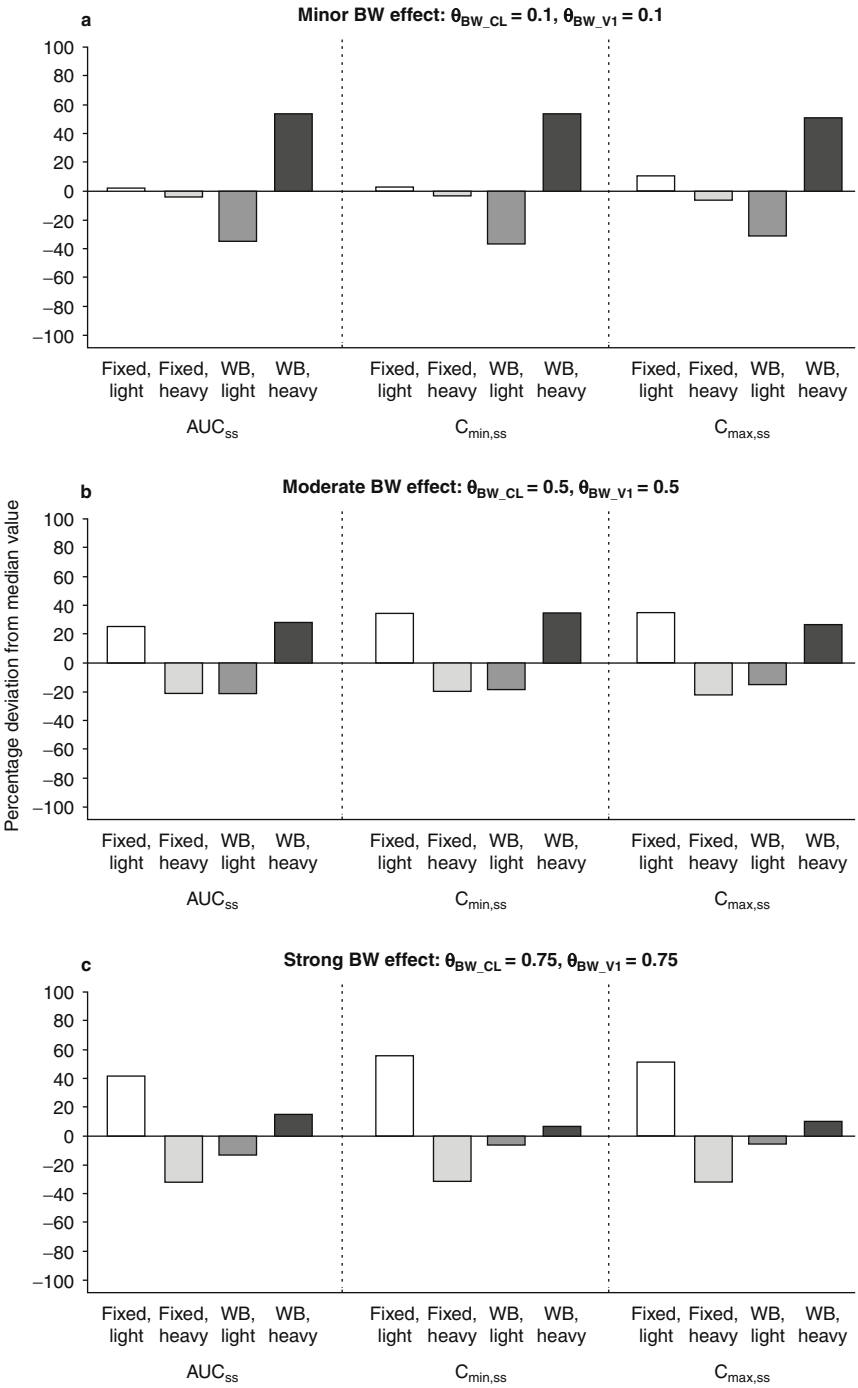

Fig. 4. Deviation of exposure from median body weight (BW) subjects: Percentage deviation of the steady-state area under the serum concentration-time curve (AUC_{ss}), the steady-state trough serum concentration ($C_{min,ss}$) and the steady-state peak serum concentration ($C_{max,ss}$) in light and heavy subpopulations compared with median exposure in the normal subpopulation are plotted in three different scenarios after fixed and body weight-based (WB) dosing: (**a**) minor BW effects on clearance (CL) and the central volume of distribution (V_1) [θ_{BW_CL} and $\theta_{BW_V1} = 0.1$]; (**b**) moderate BW effects on CL and V_1 [θ_{BW_CL} and $\theta_{BW_V1} = 0.5$]; and (**c**) strong BW effects on CL and V_1 [θ_{BW_CL} and $\theta_{BW_V1} = 0.75$].

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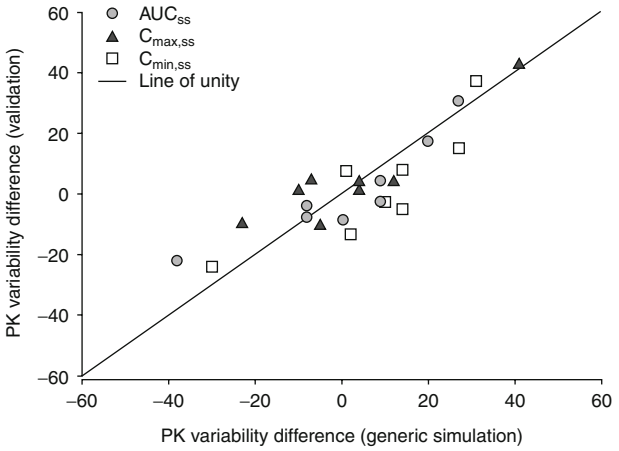

Fig. 5. Validation of the population pharmacokinetic (PK) simulation: PK variability measured by the difference of the 90% range of exposure was obtained from the population simulations using a molecule-specific model (the y-axis) against a generic model (the x-axis). The monoclonal antibodies included in the validation are bevacizumab, trastuzumab, rituximab, and GNE molecules 1, 2, 3, 4 and 5. **AUC_{ss}** = steady-state area under the serum concentration-time curve; **$C_{max,ss}$** = steady-state peak serum concentration; **$C_{min,ss}$** = steady-state trough serum concentration.

Discussion and Future Directions

In this analysis, the impact of fixed versus body weight-based dosing on drug exposure of mAbs in the adult population was systematically evaluated through theoretical simulations and a case study. A broad range of scenarios, from no effect to a strong effect of body weight on key pharmacokinetic parameters, were evaluated using a representative mAb population pharmacokinetic model. Individual simulations demonstrated that fixed dosing could lead to over-exposure in light subjects and under-exposure in heavy subjects relative to median body weight subjects, whereas body weight-based dosing can do the opposite. The population simulations highlighted the scenarios of the body weight effect (i.e. θ_{BW_CL} and θ_{BW_V1} pairs) under which either fixed or body weight-based dosing results in less IIV in the overall population or less deviation in the heavy and light subpopulations for AUC_{ss}, $C_{min,ss}$ and $C_{max,ss}$. In general, when both θ_{BW_CL} and θ_{BW_V1} are <0.5, fixed dosing results in less variability and less deviation than body weight-based dosing; when both θ_{BW_CL} and θ_{BW_V1} are >0.5, body weight-based dosing results in less variability and less deviation than fixed dosing. In the scenarios when either θ_{BW_CL} or θ_{BW_V1} is >0.5, the impact on exposure variability is different for each exposure measure. The case study demonstrated that most mAbs had little effect or a moderate body weight effect (θ_{BW_CL} and θ_{BW_V1} <5 or ~0.5). The difference of variability in exposure between fixed and body weight-based dosing is generally less than 20% and the percentage deviations for light and heavy subpopulations are less than 40%. Even in the extreme case when both θ_{BW_CL} and θ_{BW_V1} are close to 1, the difference is within ±50% for IIV in the overall population and within ±80% for the percentage deviation in exposure for light or heavy subpopulations. Results from this analysis demonstrated that exposure variability was dependent on the magnitude of the body weight effect on pharmacokinetics, and that body weight-based dosing did not always offer advantages over fixed dosing in reducing exposure variability.

It is recognized that the point estimate of the body weight exponent for an individual mAb may be influenced by available data and may vary depending on the study and/or indication. Phase I studies typically characterize pharmacokinetics in earlier cycles of therapy when steady state might not be reached, especially for mAbs with longer half-lives. The precision of the body weight exponent estimate increases with larger patient populations as mAbs advance into later stages of clinical development. Especially for some of the mAbs included in the case study, the body weight effect on pharmacokinetics was evaluated using only data from the FIH dose-escalation study (table II). The corresponding body weight exponents on CL and V_1 are preliminary and will be updated when more clinical data become available. The overall conclusions in these analyses are based on a generic model with a wide range of assumed scenarios of body weight effects, which mitigate the impact of having a less precise point estimate of the body weight effect early in clinical development. As shown in table I, for the marketed mAbs with body weight being identified as a significant covariate of CL and/or V_1 in their population analyses, θ_{BW_CL} and θ_{BW_V1} are mostly in the range of 0.3 to 0.7. The body weight exponents are smaller than those (i.e. 0.85 for CL and 1 for V_1) in the typical interspecies allometric scaling for mAbs,[29] which is likely due to the narrower body weight range (~2- to 3-fold) in human populations compared with the larger body weight range across species.

Although not extensively evaluated in the analysis, a few other scenarios should be discussed herein, which include the body weight effect on exposure in the context of larger IIV, nonlinear kinetics and body surface area (BSA)-based dosing.

Larger IIV

A comprehensive review of published and Genentech internal data suggests that most mAbs have small IIV in pharmacokinetics in the linear dose range. Therefore, 30% IIV was assumed for both CL and V_1 in the population pharmacokinetic simulations. To test the validity of this assumption, similar simulations were performed assuming 50% and 70% IIV in CL and

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V_1. The results indicate that as the IIV of pharmacokinetic parameters, contributed by other covariates or unknowns, becomes larger, the effect of body weight on exposure variability tends to be masked, making the body weight-based and fixed dosing less distinguishable from each other (data not shown). It is worth mentioning that IIV in Q and V_2 was not included in the current analysis, because clinical pharmacokinetic sampling schemes that are typically used do not usually allow a precise estimation of these parameters. Even though IIV in Q or V_2 is identifiable, it is generally small compared with IIV in CL and V_1. Therefore, the clinical implication of adding IIV in Q or V_2 to evaluate drug exposure and guide dosing selection is of limited use.

Nonlinear Pharmacokinetics

Although most mAbs display linear pharmacokinetics at therapeutic doses, several are known to have nonlinear pharmacokinetic characteristics in the therapeutic range because of predominant target-mediated disposition.[41,42] It is often observed that the IIV becomes larger for molecules in the nonlinear dose range.[1] Hence, it is expected that, in a nonlinear system, the difference in the exposure variability between fixed and body weight-based dosing would be smaller, as the large IIV and nonlinear pharmacokinetics mask the effect of body weight that mostly affects the linear clearance pathway. However, the difference in the variability of $C_{min,ss}$ between fixed and body weight-based dosing may be magnified, especially when $C_{min,ss}$ is in the concentration range where the target-mediated CL pathway is dominant (unpublished results). Therefore, the dosing strategy for molecules with therapeutic doses in the nonlinear range should be carefully evaluated on a case-by-case basis.

Body Surface Area-Based Dosing

Besides fixed and body weight-based dosing, another commonly used dosing regimen is BSA-based dosing. Genentech s internal database containing over 10 000 patients reveals a narrower range of BSA (10th 90th percentiles: 1.6 2.3 m^2) compared with body weight (10th 90th percentiles: 56 112 kg). Considering BSA is proportional to body weight $(BW)^{0.67}$,[43] it is expected that BSA-based dosing would result in less variability than either fixed or body weight-based dosing when the body weight effect is moderate (i.e. θ_{BW_CL} and θ_{BW_V1} ~0.5). However, like body weight-based dosing, BSA-based doing may not offer practical advantages compared with fixed dosing.

Most mAbs are target specific with wide therapeutic windows based on preclinical toxicity studies, the mechanism of action and the class effect. In addition, pharmacokinetic variability is generally small (30 50%).[1] Given this, a small reduction of pharmacokinetic variability may not change the therapeutic outcome. Therefore, even in the extreme case when body size has a strong effect on exposure, the difference in exposure is unlikely to have a meaningful impact on clinical outcomes for an individual subject.

In fact, for the approved mAbs, the decision to dose a mAb based on body size or fixed dosing does not appear to be based on the body weight effect on pharmacokinetics. Of the mAbs currently in clinical use, some have scientific evidence that supports their dosing regimen by the extent of the body weight effect on pharmacokinetics. For example, omalizumab, ustekinumab, efalizumab and GNE1, for which body weight has a strong effect on CL and V_1, are administered via body weight-based dosing (efalizumab and GNE1) or stratified by body weight (omalizumab and ustekinumab); and basiliximab, GNE2, GNE6 and GNE7, for which body weight has no effect or a moderate effect on CL and V_1, are administered with fixed dosing. However, a few mAbs administered with fixed dosing (e.g. golimumab and GNE3) have θ_{BW_CL} or θ_{BW_V1} greater than 0.7, in which scenarios, body weight-based dosing would reduce the IIV in exposure by at least 20% (figure 3). For subcutaneous dosing in non-oncology therapeutic areas, fixed dosing is commonly used because of its advantages in patient convenience, compliance, cost effectiveness, less risk of dosing errors, and device development (e.g. pre-filled syringes or auto-injectors). In contrast, other mAbs (i.e. bevacizumab, daclizumab, panitumumab, tratuzumab, GNE4, GNE5 and GNE9) with less body weight effect are dosed based on body weight. Most of these molecules are administered via intravenous infusion for oncology or transplantation indications, where the convenience of fixed dosing is less critical.

Taken together, the dosing strategy historically chosen for mAbs does not generally correlate well with the body weight effect on pharmacokinetics. Rather, the decision on the dosing strategy has been driven by multiple factors, including the therapeutic window, target product profile, route of administration, indication and pharmacokinetic characteristics. In some cases, decisions have been empirical. Different dosing approaches have been used for the same molecule, depending on the target indication. This flexibility in the dosing strategy corroborates with the relatively moderate difference in the IIV of exposure between body weight-based and fixed dosing, as well as the generally large therapeutic window for mAbs. It is recommended that fixed dosing should be considered as the first option in FIH studies of mAbs, when there is no prior knowledge of the body weight effect on pharmacokinetics in

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human adults, with the intent to assess this effect via thorough analyses of the generated clinical data.

While the current study focuses on a dosing strategy for mAbs in human adult populations, it is acknowledged that a dosing strategy in paediatric populations may be different. For example, the relative range of body size in the paediatric population is wider, depending on the age range, compared with the adult population. Hence, the mAb dosing in the paediatric population warrants additional investigation and body size-based dosing is generally recommended per the regulatory guidance.[44,45]

To the best of our knowledge, Wang et al.[36] published the first manuscript on fixed versus body size-based dosing of mAbs and proposed using fixed dosing in the FIH study. The objective of the current analysis was to provide further scientific support that fixed dosing in FIH studies is as appropriate as body weight-based dosing of mAbs. Our approach is unique in that it uses systematic simulations to derive thresholds for the magnitude of a body weight effect on V_1 or CL below which the impact on AUC_{ss}, $C_{max,ss}$ and $C_{min,ss}$ is negligible. The simulation can be used as a guide during drug development, when the first population pharmacokinetic results are available and a decision on the dosing strategy for subsequent phases of clinical development is made. Therefore, this study provides a comprehensive understanding of how the dosing strategies affect exposure variability under multiple scenarios of the body weight effect on pharmacokinetics, and offers a practical implication for mAb drug development. The results and conclusions from this study can be generalized for typical mAbs with linear kinetics.

In light of the comprehensive analysis presented in this manuscript, a decision tree is proposed (figure 6) to help guide the dosing strategy selection for mAbs through clinical development in adult patient populations. The dosing strategy in the FIH study should be determined based on integrated preclinical knowledge of pharmacology, efficacy and safety. Although the body weight effect on pharmacokinetics in humans cannot be predicted prior to the FIH study, one can obtain the safety information and estimates of the efficacious exposure range from preclinical assessments. These data will provide insight into whether the clinical candidate is expected to have a wide therapeutic window or not. As fixed dosing offers practical advantages and allows the feasibility of device development for subcutaneous injections, it is recommended as the first option as long as the mAb is predicted to have a reasonably wide therapeutic window in humans. The body weight effect on pharmacokinetics will later be evaluated using population analysis when sufficient data become available from early-phase clinical trials. The outcome from this later analysis, in combination with safety and efficacy information, will determine whether fixed dosing is optimal or if a modification of dosing is necessary to maximize the likelihood of successful therapeutic drug development. The dosing decision in late-phase drug development should largely be driven by the therapeutic window and, to a lesser extent, by the body weight effect on pharmacokinetics. For mAbs with a wide therapeutic window regardless of the body weight effect on pharmacokinetics, either dosing strategy is feasible although fixed dosing is generally preferred for practical reasons. For mAbs with a narrow therapeutic window and little effect or a moderate body weight effect (i.e. θ_{BW_CL} and θ_{BW_V1} <0.5 or ~0.5) fixed dosing may be considered after careful evaluation of safety data. For mAbs with a narrow therapeutic window and a strong body weight effect (i.e. θ_{BW_CL} and θ_{BW_V1} >0.5), a single fixed dosing regimen may not be optimal and the dosing regimen should be carefully evaluated case by case, taking into account the known exposure, efficacy and safety relationships.

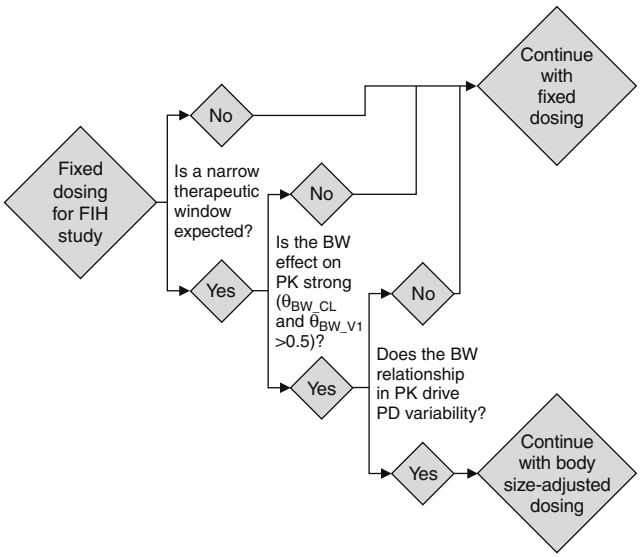

Fig. 6. Proposed decision tree for dosing monoclonal antibodies in adult patients during clinical drug development. θ_{BW_CL} = BW effect on clearance; θ_{BW_V1} = BW effect on the central volume of distribution; **BW** = body weight; **FIH** = first in human; **PD** = pharmacodynamic; **PK** = pharmacokinetics.

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