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Fixed Dosing Versus Body Size–Based Dosing of Monoclonal Antibodies in Adult Clinical Trials

Diane D. Wang, PhD, Shuzhong Zhang, PhD, Hong Zhao, PhD, Angela Y. Men, PhD, and Kourosh Parivar, MS

Although without clear scientific rationale, body size–based dosing is often used for administering monoclonal antibodies (mAbs). This simulation study compared the performance of body size–based and fixed dosing in reducing pharmacokinetic (PK) and/or pharmacodynamic (PD) variability in adults for 12 mAbs with published population PK and/or PD models. At the population level, 95th percentile intervals of concentration-time profiles, distribution, and variability of exposure for 1000 subjects after both dosing approaches were examined. At the individual level, the difference between the exposures of patients with extreme body sizes from the typical exposure following both approaches was compared. The results show that the 2 dosing approaches perform similarly across the mAbs investigated with fixed dosing being better for some mAbs and body size–based dosing being better for the others. Based on this finding, we recommend using fixed dosing in first-in-human (FIH) adult studies because it offers other advantages. When sufficient data become available, a full assessment of body size effect on PK/PD should be conducted to determine the optimal dosing approach for phase 3 trials. Other factors that may affect the selection of dosing approach were also discussed. Dosing approach for mAbs in the pediatric population is out of the scope of this study.

Keywords: *Fixed dosing; body size–based dosing; body weight; body surface area; biologics; monoclonal antibodies; population pharmacokinetics; pharmacodynamics*

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Whether a drug should be administered based on a patient's body size, such as body weight (BW) and body surface area (BSA), mainly depends on the effect of the body size on the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug, as well as its therapeutic window. A good dosing strategy should provide reduced interpatient variability in PK and/or PD and ultimately optimize therapeutic outcome. For drugs with a wide therapeutic window, a fixed dosing approach is generally chosen for adult patients, regardless of the influence of body size on PK and PD properties due to its convenience, better compliance, less risk for medical errors, and cost-effectiveness. On the other hand, for drugs with a narrow therapeutic window, the effect of body size, as well as other influential factors, on PK and PD should be carefully evaluated in order to select a dosing strategy which optimizes the risk/benefit ratio.

Fixed dosing is the most common dosing approach for small molecule drugs in adult patients. Biologic products, such as monoclonal antibodies (mAbs), are however often dosed based on body size. In the past decade, there has been a significant increase in the development of biologics. Currently, a total of 20 mAb therapeutics have been approved by the Food and Drug Administration (FDA), and many others are under development. Among the 18 approved non-radioimmunotherapeutic mAbs, 12 products are administered in adult patients based on a patient's body size (Table I). In mAb development, especially for first-in-human (FIH) trials, the current thinking

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Table I Food and Drug Administration (FDA)–Approved Monoclonal Therapeutics (excluding radioimmunotherapeutics) and Their Dosing Approaches for Adult Patients

mAb	Brand Name	Approval Date	Type	Target	Dosing Approach
Abciximab	ReoPro	1994	Chimeric	Glycoprotein Iib/IIIa	mg/kg
Adalimumab	Humira	2002	Human	TNFα	mg
Alemtuzumab	Campath	2001	Humanized	CD52	mg
Basiliximab	Simulect	1998	Chimeric	IL-2 receptor a	mg
Bevacizumab	Avastin	2004	Humanized	VEGF	mg/kg
Cetuximab	Erbitux	2004	Chimeric	EGFR	mg/m^2
Daclizumab	Zenapax	1997	Humanized	IL-2 receptor a	mg/kg
Eculizumab	Soliris	2007	Humanized	complement system protein C5	mg
Efalizumab	Raptiva	2002	Humanized	CD11a	mg/kg
Infliximab	Remicade	1998	Chimeric	TNFα	mg/kg
Muromonab-CD3	Orthoclone OKT3	1986	Murine	CD3 receptor	mg
Gemtuzumab Ozogamicin	Mylotarg	2000	Humanized	CD33	mg/m^2
Natalizumab	Tysabri	2006	Humanized	VLA4 receptor	mg
Omalizumab	Xolair	2004	Humanized	IgE	mg, but stratified on IgE levels and body weight
Palivizumab	Synagis	1998	Humanized	F protein of RSV	mg/kg
Panitumumab	Vectibix	2006	Human	EGFR	mg/kg
Rituximab	Rituxan, Mabthera	1997	Chimeric	CD20	mg/m^2
Trastuzumab	Herceptin	1998	Humanized	ErbB2	mg/kg

is that body size–based dosing should provide more consistent exposure across patients and is therefore recommended. However, the validity of this current thinking has not been systematically examined.

Based on the assumption that patients with larger body size have a larger volume of distribution and a higher drug-metabolizing capacity, small molecule oncology drugs with narrow therapeutic windows, such as classic cytotoxic agents, have been mostly administered based on patients' BSA.[1,2] It has been generally perceived that dosing these cytotoxic agents "precisely" based on patients' body size should minimize interpatient variability in PK and thereby optimize their therapeutic outcome.[2] However, in addition to body size, many other factors, such as genetic polymorphisms in drug-metabolizing enzymes and transporters, concomitant medications, and food and smoking habits, could also affect the PK of a drug.[3-5] As such, the interpatient variability in the PK of most cytotoxic agents is still in the order of 25% to 75%, even following a BSA-based dosing.[2] Therefore, many studies have been conducted to evaluate the necessity of BSA-based dosing for oncology drugs.[2,6-12] Interestingly, these studies showed that the clinical benefit of BSA-based dosing is minimal in most cases. For example, in a retrospective study of 33 investigational anticancer drugs, the clinical benefit of BSA-based dosing was considered to be of significance for only 5 drugs.[11] Therefore, it has been advised that fixed dosing should be implemented in the development of new investigational drugs unless a significantly better alternative exists.

Although the validity of the aforementioned assumption for small molecule oncology drugs has been questioned and revisited, the clinical relevance of body size–based dosing of mAbs remains largely unknown. The latter should be examined separately, considering that the sources for the variability in exposure are likely to be different between mAbs and small molecules due to their different distribution and elimination mechanisms.[13] Unlike small molecules, which are generally distributed into tissues via diffusion and eliminated through metabolism and renal excretion, mAbs extravasate mainly by convection and are eliminated by catabolism and/or target-mediated clearance. The FcRn receptor plays an important role in protecting IgG molecules from catabolism.[13] For mAbs undergoing target-mediated clearance, the binding affinity of the mAb to the target and the extent of the target expression could be important determinants of mAb clearance. With increased mAb development in recent years, a significant amount of PK and PD information for mAbs becomes available. This provides us a great

opportunity to evaluate the 2 dosing strategies for mAbs. The objectives of the present study are therefore to (1) systematically evaluate in adults the performance of body size–based dosing and fixed dosing for mAbs and (2) recommend a dosing strategy for clinical trials conducted in adults in different stages of mAb development. Dosing approach for mAbs in the pediatric population is out of the scope of this study.

METHODS

Data Collection

Data used for this analysis were mAb studies published in peer-reviewed journals. The selection criteria included the availability of population PK (or PD) models for adult patients and a well-established relationship or lack of it between the PK (or PD) parameters and body size. Special attention has been paid to the uncertainty of the estimation for the parameters describing the effect of body size on PK and/or PD parameters.

Population PK and PD Models

The population PK and PD models of the selected mAbs were obtained from published reports. General properties of these population PK and PD models and effects of body size measures, that is, BW, BSA, or ideal body weight (IBW), on the PK and PD parameters are described in Table II.

Mixed-effect models have been used to describe the PK or PD of all 12 mAbs. The *j*th observation for the *i*th individual was given by $y_{ij} = f(\theta_i, t_{ij})(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$, where θ_i is a set of the PK or PD parameters for the *i*th individual; ε_{1ij} and ε_{2ij} are intrasubject variability normally distributed with a mean of zero, and variance of σ_1^2 and σ_2^2, respectively. θ_i was further described by $\theta_i = g(z_i, \theta) + \eta_i$, where z_i is a set of fixed effects, and θ is a set of typical population PK/PD parameters; η_i is the intersubject variability with a variance of Ω^2 and mean of zero. Simulation studies were conducted using NONMEM (version VI; GloboMax, Hanover, Maryland).

PK and PD Simulation

Population performance. To evaluate the population performance, Monte Carlo simulation was conducted using the full PK and PD model reported for each mAb to construct the concentration-time (c-t) profiles following both fixed dosing and BW/BSA–based dosing. The selection of BW- or BSA-based dosing approach is based on the dosing approach recommended in the labeling for marketed products or the dosing approach used in the reported clinical trials for the mAb therapeutics under development. For all simulation studies, 1000 subjects were simulated per treatment group with 30 sampling points for each subject. The sampling points were chosen based on the PK or PD properties of mAbs, and the same sampling schedule was used for both dosing approaches (fixed dosing and body size–based dosing).

For each mAb study, the values of demographic variables that had been identified as covariates of the PK or PD parameters of the mAbs were randomly generated using S-PLUS 7.0 (TIBCO, Palo Alto, California). With the exception of BW, these variables were assumed to follow either normal or lognormal distributions with the median, range, and standard deviation of each covariate in close proximity to those reported in the corresponding population PK publication. In particular, BSA values were generated assuming normal distribution[14] with a median of 1.82 m^2 and a standard deviation selected by trial and error so that the BSA of the simulated population was in the range of 1.2 to 2.4 m^2 (Figure 1B).

A different approach was used to generate BW values. Historical data have shown that BW does not follow normal distribution while transformation of BW by a power function $Z = BW^{\alpha}$ gives a better approximation to normal distribution.[15] The generation of BW was therefore based on this power equation with $\alpha = -.5$. This α value has been shown to be able to adequately describe the right tail of natural BW distribution.[15] The generated BW (1000 values) has a median of 75.7 kg and a range of 38.8 to 187.2 kg (Figure 1A), which are similar to those reported for mAb studies.

When both BW and BSA are covariates of the PK or PD parameters, as for pertuzumab, BW and BSA values were assigned to the subjects in such a way that the rank orders of BW and BSA are exactly the same (ie, the subject with the highest BW also has the highest BSA and vice versa). The same approach was used for the assignment of BW and IBW as for cetuximab.

The dose of fixed dosing approach was set to the dose that would be given to a subject with median BW/BSA by BW/BSA–based dosing. To avoid negative drug concentration values in simulation, the additive residual error in efalizumab, infliximab, and matuzumab PK models was set to zero. This modification should only make the comparison more stringent because of the reduced overall PK variability for both dosing approaches.

Table II Population Pharmacokinetics/Pharmacodynamics (PK/PD) Models for the Selected Monoclonal Antibodies

mAb	Type	Dosing	Structure Model	Covariates, Median (Range)	Covariate Model	N	Reference
Rituximab	Chimeric IgG1	mg/m^2	2-CMT, linear	BSA: 1.72 (1.41-2.35)	CL = CL*x (BSA/1.72)$^{1.02}$ V1 = V1*x(BSA/1.72)$^{0.73}$	102	20
Omalizumab	Humanized IgG1	Based on IgE baseline and BW	TMD	BW: 61.1 (39-150)	CL/F = CL/F* x(BW/61.1)$^{0.911}$ V = V*x(BW/61.1)$^{0.658}$	202	16
Efalizumab	Humanized IgG1	mg/kg	1-CMT, linear	BW: 91 (43-192)	CL/F = CL/F* x(BW/91)$^{0.754}$	1088	21
Pertuzumab[a]	Humanized IgG1	mg/kg	2-CMT, linear	BW: 69 (45-150.6) BSA: 1.73 (1.40-2.53)	CL = CL*x (BW/69)$^{0.587}$ V1 = V1*x (BSA/1.72)$^{1.16}$	153	22
Bevacizumab	Humanized IgG1	mg/kg	2-CMT, linear	BW: 74 (49-114)	CL = CL*x(BW/74)$^{0.368}$ V1 = V1*x(BW/74)$^{0.411}$	491	23
Matuzumab[a]	Humanized IgG1	mg	2-CMT, both linear and nonlinear elimination	BW: 71 (44-125)	CL_{linear} = CL_{linear}*x (1+0.0087x (BW-71)) V1 = V1*x(1+0.0044x (BW-71))	90	24
Sibrotuzumab[a]	Humanized IgG1	mg/m^2 or mg	2-CMT, both linear and nonlinear elimination	BW: 75 (42-134)	CL_{linear} = CL_{linear}*x (1+0.0182x(BW-75)) V1 = V1*x(1+0.0125 x(BW-75)) $V2_r$ = V2*x(1+0.0105 x(BW-75)) Vmax = Vmax*x (1+0.00934x(BW-75))	60	25
Cetuximab	Chimeric IgG1	mg/m^2 Michaelis-Menten elimination	2-CMT,	BW: 60 (34-113)	Vmax = Vmax*x (1+0.0108x(IBW-64)) IBW: 64.2 (43.3-81.3) V1 = V1*x (1+0.0083x(BW-60))	143	26
Golimumab[a]	Human IgG1	mg/kg	2-CMT, linear	BW: 72.3 (53-153.8)	V1 = V1* x(BW/74)$^{0.86}$	36	27
Infliximab	Chimeric IgG1	mg/kg	2-CMT, linear	BSA: 1.94 (1.37-2.6)	V1 = V1* x(BSA/1.94)$^{0.744}$	274	28
Trastuzumab	Humanized IgG1	mg/kg	2-CMT, linear	BW: 70 (42-119)	V1 = V1* x(BW/65)$^{0.556}$	476	29
Alemtuzumab	Humanized IgG1	mg	2-CMT Michaelis-Menten elimination	BW: ? (45-167)	WT is not a covariate	67	30

BW, body weight; BSA, body surface area; IBW, ideal body weight; N, number of patients from which the PK and/or PD data were used for population PK or PD modeling.
a. Antibodies not in market yet.
*Parameter value without body size correction.

Individual performance. To evaluate the individual performance, the PK profiles for the subjects with typical, low extreme, or high extreme BW/BSA measures were simulated. The typical value of BW/BSA used in this study was 75.7 kg/1.8 m^2. The low and high extremes of BW/BSA values were 40 kg/1.3 m^2 and 140 kg/2.3 m^2, respectively. For other covariates, typical values were used. The intersubject variability and residual error were all set to zero.

Performance Evaluation

Population performance. Population performance was evaluated by comparing the following metrics

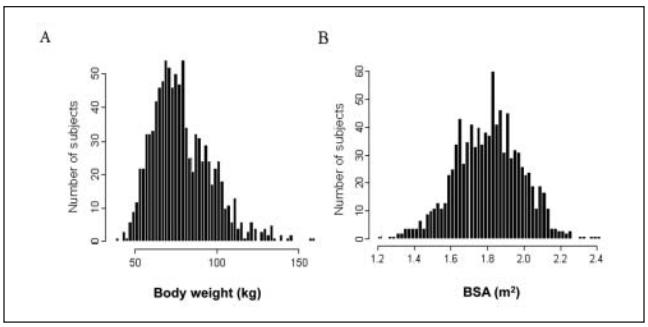

Figure 1. The distribution of simulated body weight (A) and body surface area (B).

resulting from the 2 dosing approaches: (1) the 95th percentile intervals (the interval between 2.5th and 97.5th percentile) of the drug c-t profiles of the 1000 subjects; (2) the distribution of AUC and Cmax; and (3) the intersubject variability (expressed as CV%) of AUC and Cmax.

Cmax for each subject was determined as the maximal concentration from the simulated c-t profile of the subject. When the mAb exhibits linear PK, the AUC was calculated by dose/CL. When the mAb exhibits nonlinear PK, the AUC was generated by integration of the c-t curve using NONMEM (GloboMax).

Individual performance. To evaluate the individual performance, the percentage difference in the exposure between subjects with extreme body sizes and typical body size was compared for the 2 dosing approaches.

The dosing approach that produced narrower 95th percentile intervals of PK and/or PD profiles, narrower shape and shorter tails of AUC and Cmax distribution curves, and less intersubject variability of AUC and Cmax provides a better population performance. The dosing approach that resulted in a smaller difference in PK and PD exposure between subjects with extreme body size and typical body size has better individual performance. The dosing approach with better performance at both population and individual levels is considered a better approach.

RESULTS

Data

Twelve mAbs were identified based on the data collection criteria specified in the Method section and listed in Table II. The relative standard error (RSE %) of the estimate for body size effect ranged from 14.7% to 28.2% for clearance and 12% to 40% for volume distribution. When standard error of the estimate was not reported, none of the confidence intervals of parameter estimates for body weight effect included zero for both clearance and volume distribution.

Dosing Approach Performance

Population performance. The median and the 95th percentile intervals of the simulated c-t profiles following the 2 dosing approaches are compared in Figure 2. As expected, the median c-t profiles were superimposed on each other for all the mAbs studied, as the median dose for the 2 dosing approaches is the same. The focus of the comparison is therefore the 95th percentile intervals of the c-t profiles. While body size–based dosing results in somewhat narrower 95th percentile intervals for some mAbs, such as sibrotuzumab and omalizumab, fixed dosing approach does a better job for others like bevacizumab, golimumab, and alemtuzumab. Overall, the 95th percentile intervals do not differ remarkably between the fixed and BW/BSA–based dosing approaches across all the 12 mAbs studied.

The distribution curves of AUC and Cmax following the 2 dosing approaches are presented in Figure 3 and Figure 4, respectively. It is observed that the 2 dosing approaches resulted in different distribution curves of AUC and Cmax for some mAbs, but these differences are generally small. In addition, neither of the dosing approaches shows a clear advantage in terms of reducing AUC or Cmax variability.

The intersubject variability of exposure following the 2 dosing approaches is presented in Figure 5. Again, neither approach shows any obvious advantage. Body size–based dosing results in less variability in AUC for 5 mAbs, while fixed dosing produces less variability for the other 7 mAbs. The average variability in AUC of all the 12 mAbs studied is similar following the 2 dosing approaches (42.4% by fixed dosing vs 44.2% by BW/BSA–based dosing). Similar results have also been obtained for Cmax (30.1% by fixed dosing and 30.3% by BW/BSA–based dosing).

Individual performance. The results of individual performance of the 2 dosing approaches are shown in Figure 6. The fixed dosing performs better than the body size–based dosing with smaller percentage difference in AUC for 7 of 12 mAbs and in Cmax for 5 of 12 mAbs between subjects with extreme body sizes and typical body size. Another

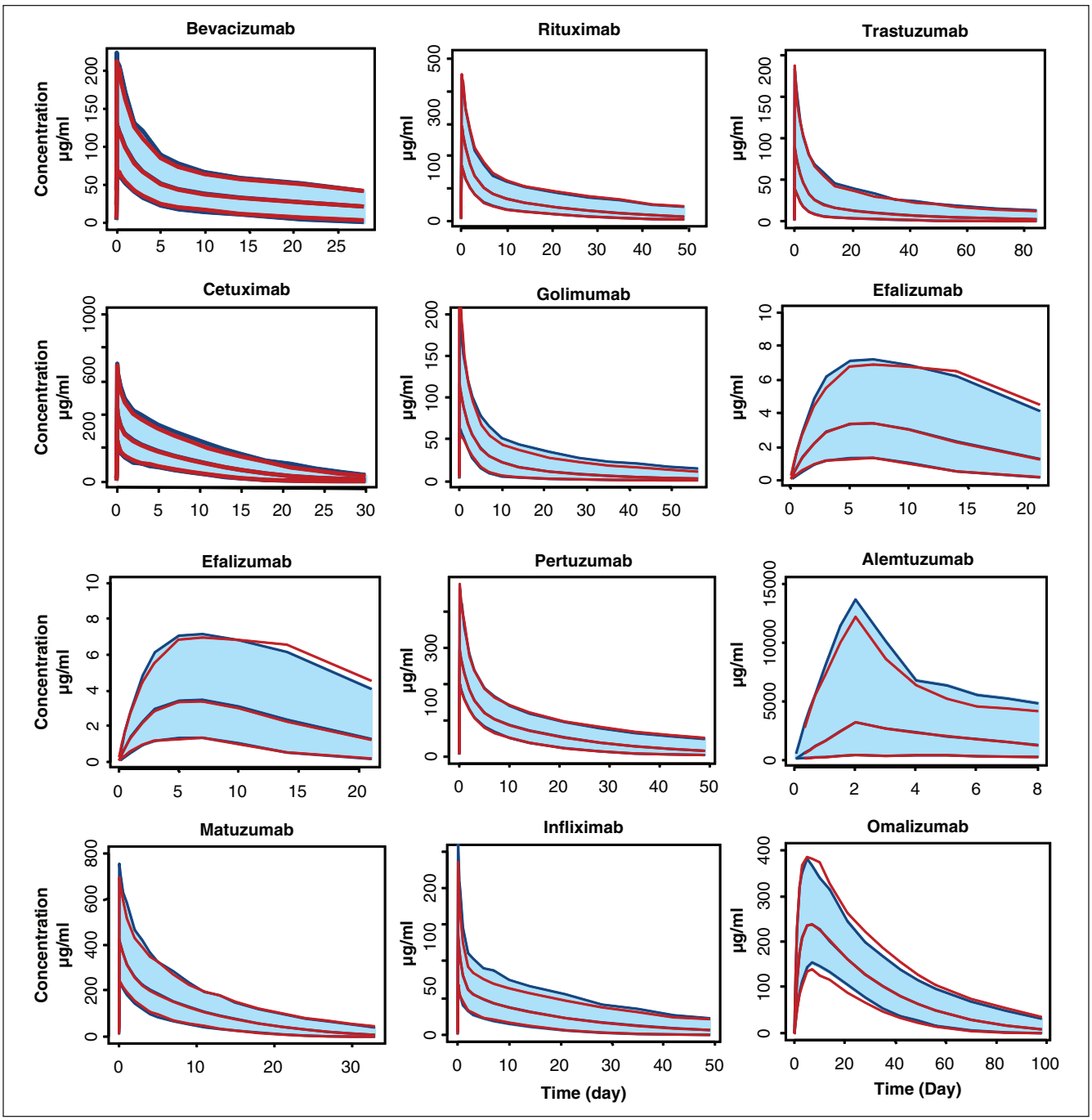

Figure 2. The median, 97.5th, and 2.5th percentiles of the simulated concentration-time profiles of 1000 subjects following a single fixed (red lines) and body weight/body surface area (BW/BSA)–based (blue lines) dose. The shaded area represents the 95th percentile interval of the simulated concentrations after a BW/BSA–based dose.

observation is that body size–based dosing tends to overdose patients with large body size while underdose patients with small body size. The opposite is true for fixed dosing, that is, overdose patients with small body size but underdose patients with large body size.

For omalizumab, both PK and PD models have been established.[16] Therefore, the performance of

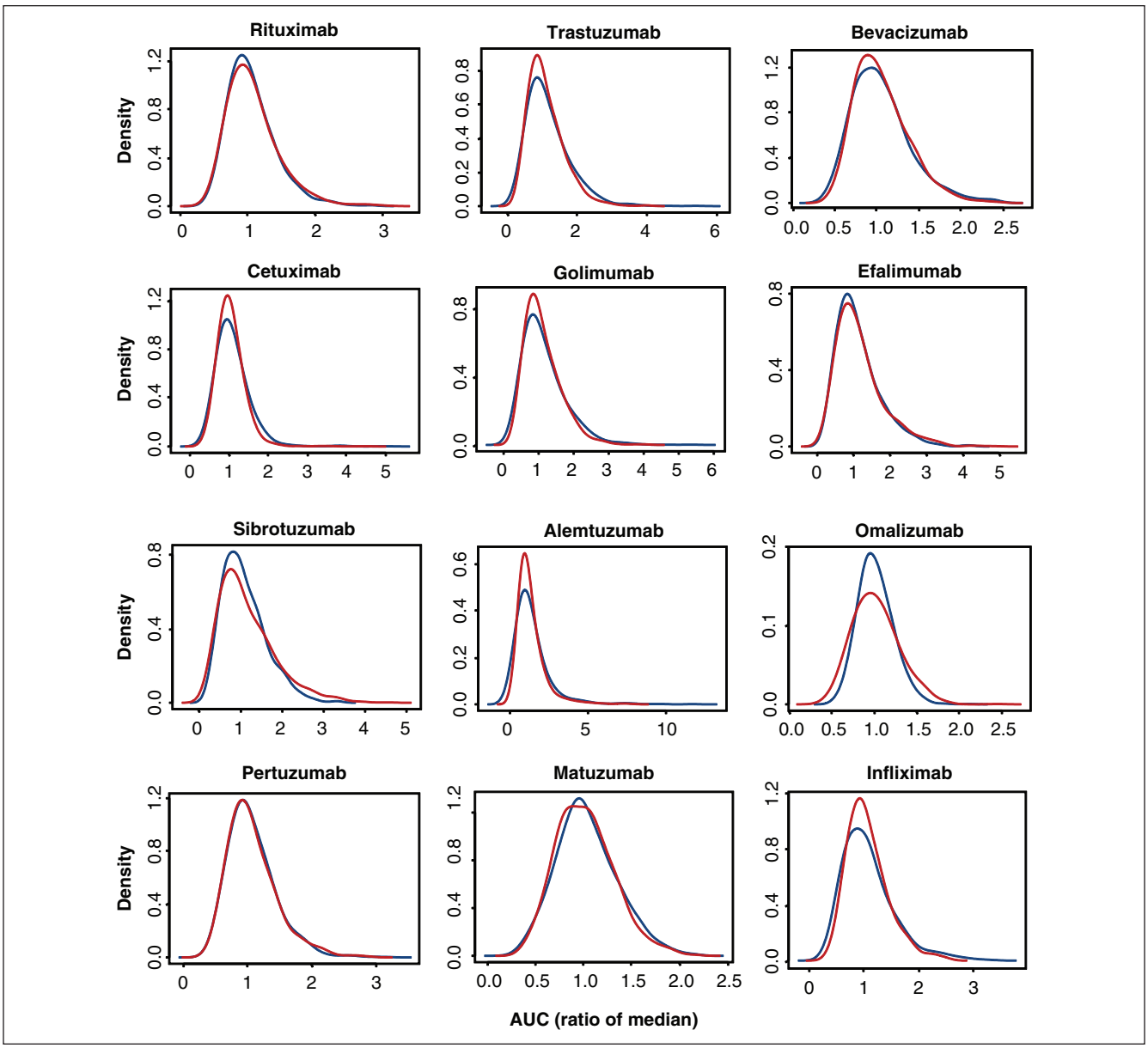

Figure 3. Distribution of the simulated AUC values of 1000 subjects following a single fixed (red line) and body weight/body surface area (BW/BSA)–based (blue line) dose.

each dosing approach has also been evaluated for the PD endpoint–free IgE levels as shown in Figure 7. Compared with the differences in the PK performance of the 2 dosing approaches, the differences in their PD performance are smaller in all measures.

DISCUSSION

When a candidate mAb molecule enters clinical development after showing promising results from preclinical testing, the starting dose for the FIH trial is generally derived from the no observed adverse effect level (NOAEL) or the minimal anticipated biological effect level (MABEL) determined in relevant preclinical species on a milligram per kilogram (mg/kg) basis. This mg/kg dosing approach has thus often been naturally adapted to clinical studies and eventually leads to body size–based dosing for most of the marketed mAb products. Another important factor that has made body size–based dosing a common

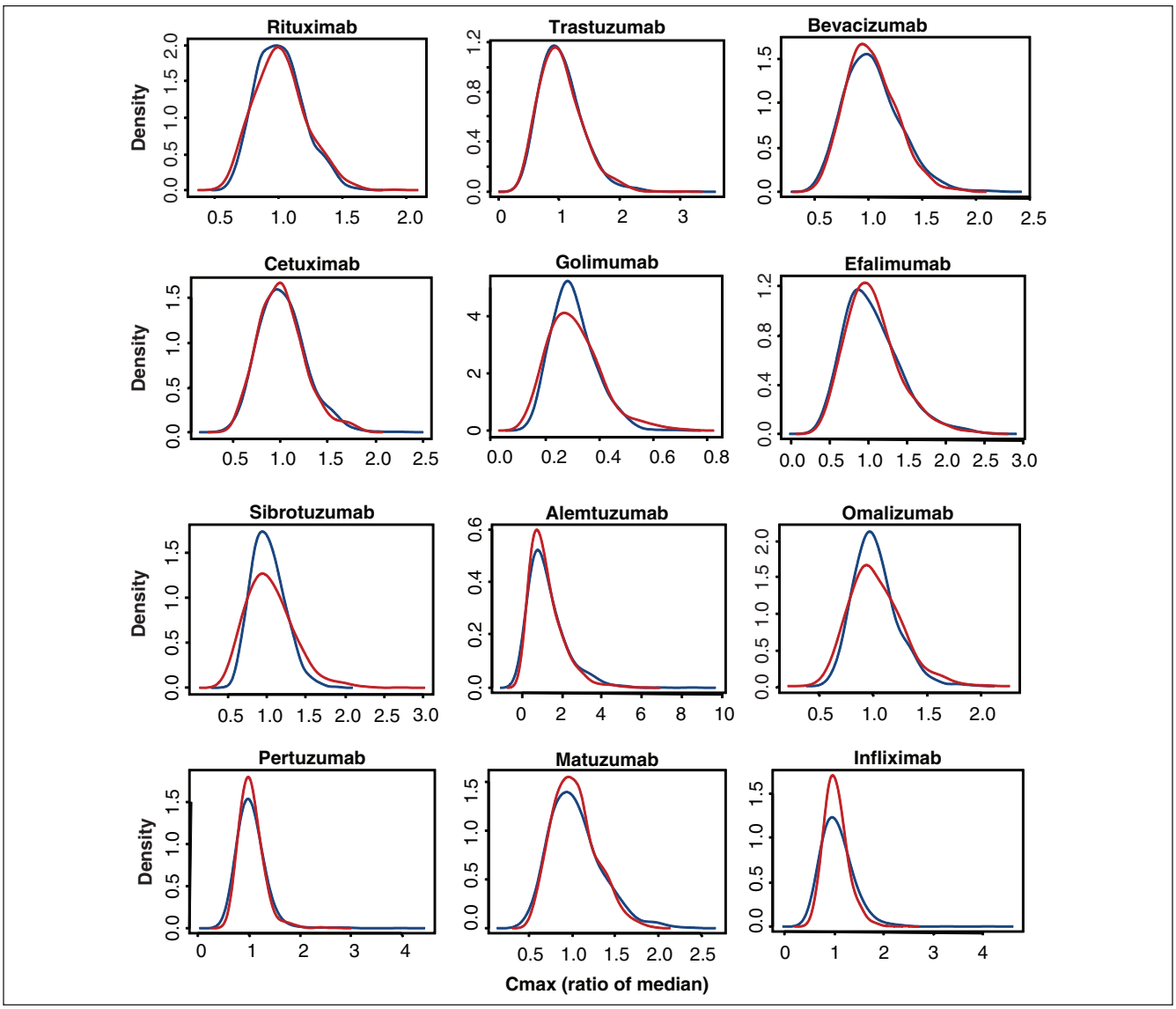

Figure 4. Distribution of the simulated Cmax values of 1000 subjects following a single fixed (red line) and body weight/body surface area (BW/BSA)–based (blue line) dose.

dosing approach is the perception that such a doing approach would provide less variable exposure levels across patients. The present simulation study evaluated the validity of this assumption for mAbs. The results may be used as the basis to recommend an appropriate dosing approach for mAb FIH studies.

Effect of Dosing Approach on Exposure of mAbs

Among the 12 mAbs investigated, body size measures (BW, BSA, or IBW) have been found to be covariate(s) of one or more of the PK parameters for 11 mAbs (Table II). The PK parameters affected by body size include CL, V1, V2, and Vmax. However, whether the effect of body size on PK parameters warrants a dose adjustment based on body size depends on the significance of such effects on PK and/or PD profiles and ultimately the clinical outcomes. The population performance of a dosing approach provides an overall picture of PK and/or PD variability across the whole patient population. In other words, how well does a dosing approach accommodate the entire patient population? The individual performance evaluates the effect of body size on exposure measures under

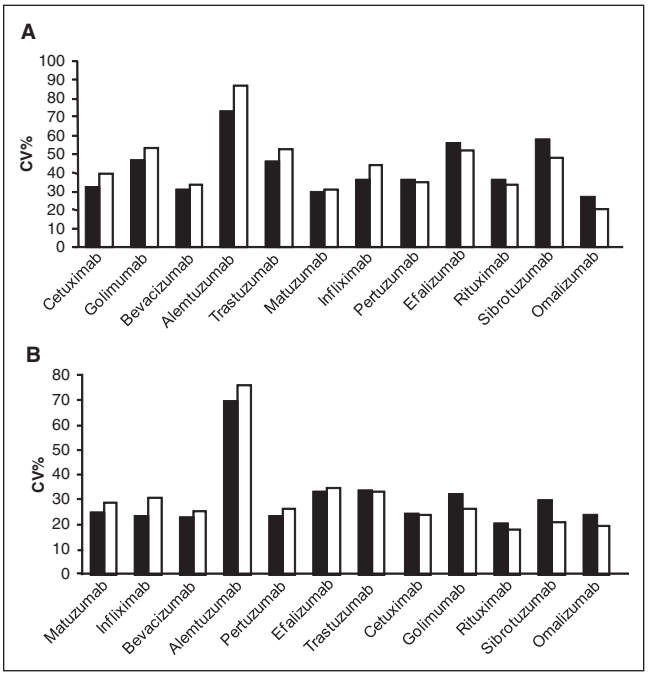

Figure 5. Comparison of the variability of simulated AUC (A) and Cmax (B) of 1000 subjects after receiving a single fixed (solid bar) and body weight/body surface area (BW/BSA)–based dose (open bar).

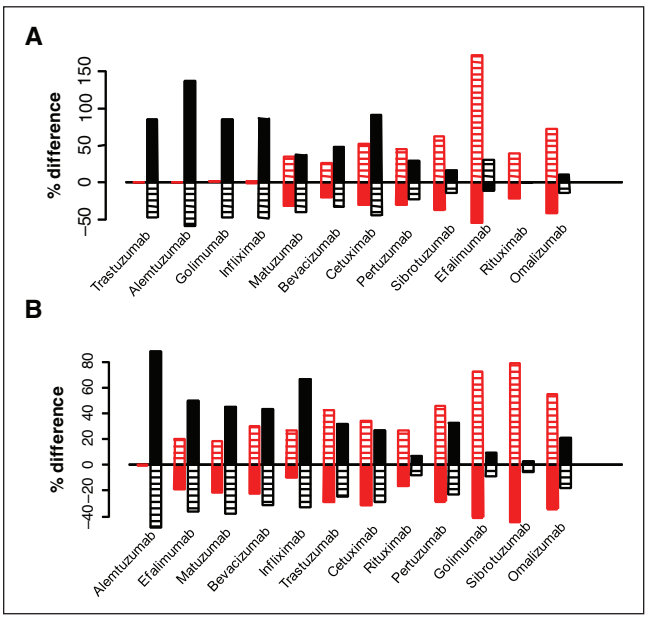

Figure 6. Comparison of the deviation of AUC (A) and Cmax (B) for subjects with low (open bar) and high (solid bar) extreme body weight/body surface area (BW/BSA) values from the typical exposure after fixed (red) and BW/BSA–based (black) dosing.

extreme conditions. The amount of overdose and underdose to patients with extreme body size is of particular concern both in drug development and for regulatory approval as it may have significant efficacy and safety implications.

In contrast to the expectation that body size–based dosing should give rise to less variability in exposure measures, very similar performances have been observed for the 2 dosing approaches at both population and individual levels in the current study. This can partly be explained by the fact that the relationships between body size and PK or PD parameters of mAbs are rarely shown to be body size proportional. An exponent of 1 for a power function covariate model describes a proportional change of a PK parameter with change in the covariate. As shown in Table II, the exponent of the covariate model for body size effect on the CL of a linear elimination pathway ranges from 0 (body size was not a covariate) to 1.02. Which dosing approach is better depends on how steep the relationship is between CL and body size, that is, the value of the exponent. Figure 8 shows the percentage difference in AUC values between subjects with extreme BW and typical BW as a function of the exponent simulated using pertuzumab PK parameters. This relationship applies to any drug because the percentage difference in AUC values depends only on the ratio of the extreme BW to the typical BW and the values of the exponent as derived below:

Fixed dosing:

$$Difference = \frac{AUCex - AUCty}{AUCty} = \frac{\frac{Dose}{\overline{CL}\bullet\left(\frac{BW}{\overline{BW}}\right)^{a}} - \frac{Dose}{\overline{CL}}}{\frac{Dose}{\overline{CL}}}$$

$$\%Difference = 100\%\bullet\left(\left(\frac{\overline{BW}}{BW}\right)^{a} - 1\right)$$

BW-based dosing:

$$Difference = \frac{AUCex - AUCty}{AUCty} = \frac{\frac{\overline{D}\bullet\left(\frac{BW}{\overline{BW}}\right)}{\overline{CL}\bullet\left(\frac{BW}{\overline{BW}}\right)^{a}} - \frac{\overline{D}}{\overline{CL}}}{\frac{\overline{D}}{\overline{CL}}}$$

$$\%Difference = 100\%\bullet\left(\left(\frac{\overline{BW}}{BW}\right)^{a-1} - 1\right)$$

where AUCex and AUCty are the AUC values for patients with extreme BW and typical BW ($\overline{BW}$),

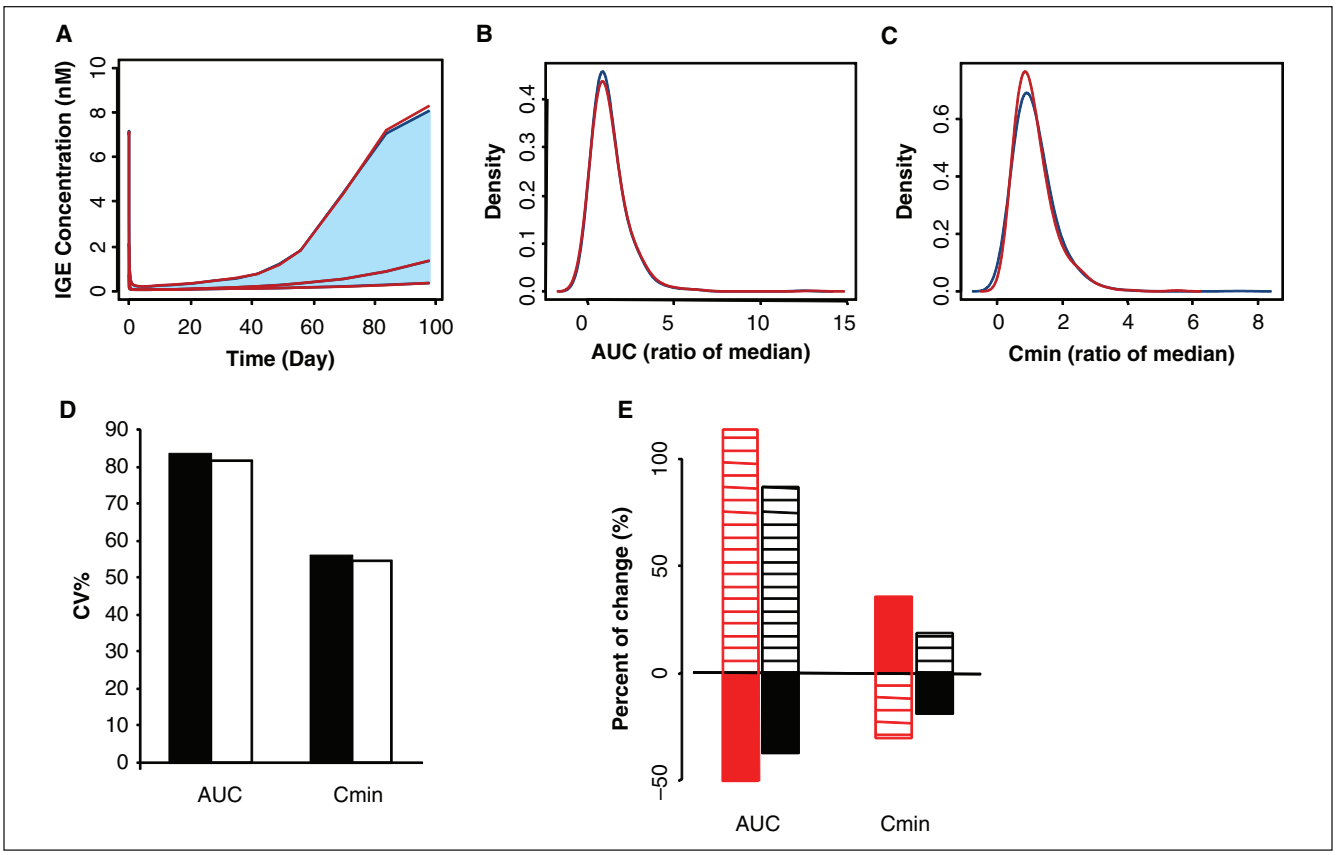

Figure 7. (A) The median and 95th percentile interval of simulated free IgE concentration-time profile after a fixed (red) and a body weight (BW)–based (blue) dose. (B) The distribution of free IgE AUC (the area between free IgE concentration-time curve and the free IgE baseline) after fixed (red) and BW-based (blue) dosing. (C) The distribution of free IgE Cmin after fixed (red) and BW-based (blue) dosing. (D) The intersubject variability of AUC and Cmin across 1000 subjects after fixed (solid bar) and BW-based (open bar) dosing. (E) Deviation of AUC and Cmin of free IgE for subjects with low (open bar) and high (solid bar) extreme BW from the typical value after a fixed (red) and BW-based (black) dose of omalizumab.

respectively, Dose is the total dose amount, $\overline{CL}$ is the CL for patients with ($\overline{BW}$), α is the exponent of the power function for BW effect on CL, and $\overline{D}$ is the dose for patients with $\overline{BW}$.

The low extreme, typical, and high extreme BW values used in this simulation were set to 40, 75, and 140 kg, respectively (Figure 8A). It can be seen that fixed dosing works the best when CL is not affected by BW ($\alpha = 0$) and BW-based dosing works the best when α equals to 1, and the 2 dosing approaches perform the same when α equals to .5. It is also illustrated that fixed dosing provides less variability in exposure when $\alpha < .5$ while this is true for BW-based dosing when $\alpha > .5$. The upper and lower bound of the shaded area in Figure 8A represents ±20% AUC difference between patients with extreme BW and those with typical BW. For mAbs with α values less than .32, fixed dosing will keep the patients with extreme BW within the boundary if other covariates are kept the same. On the other hand, BW-based dosing will provide the same benefit for molecules with α values greater than .68. If the α value of an mAb falls between .32 and .68, neither approach can keep the AUC difference less than 20%. Depending upon the α value, one dosing approach could have an advantage over the other. However, more often than not, the 2 dosing approaches lead to similar variability in drug exposure across the patient population, although they tend to overdose or underdose different body size patient groups (fixed dosing tends to overdose small body size patients, while body size–based dosing tends to overdose large body size patients).

Figure 8B shows the result when a different median BW (90 kg) was used while extreme BW values remain the same. Although the shape of the curves looks different, a similar conclusion can be made

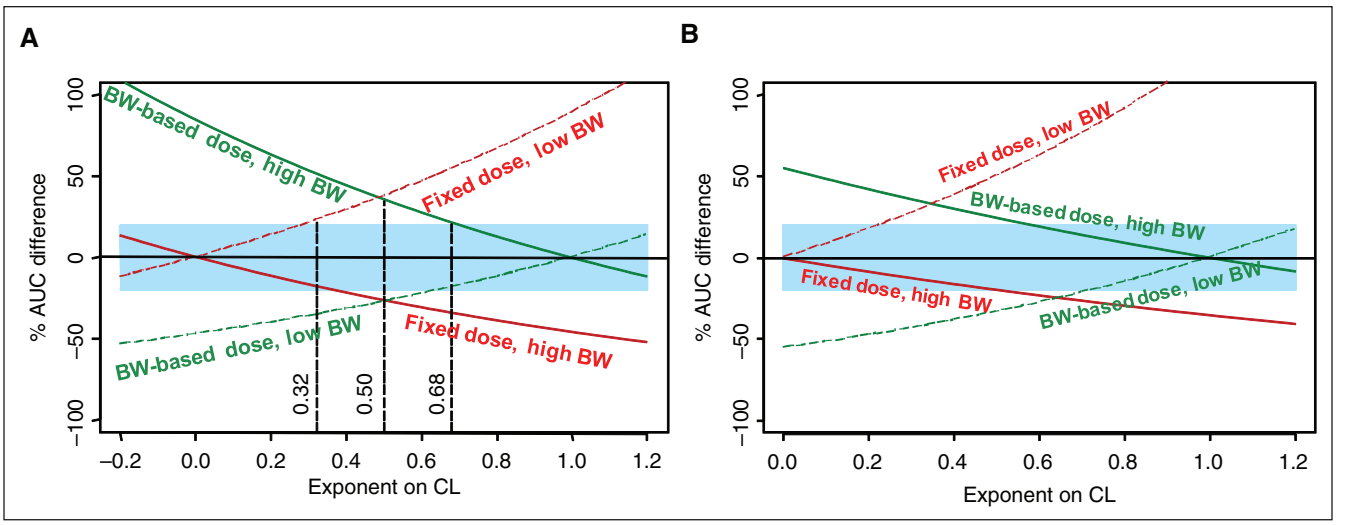

Figure 8. The percentage difference of AUC for patients with extremely low body weight (BW) (40 kg, colored broken lines) and extremely high BW (140 kg, colored solid lines) from those for patients with a median BW of 75 kg (A) and 90 kg (B) as a function of α (range, 0-1.2) for fixed (red) and BW-based (green) dosing, assuming $\overline{CL} = \overline{CL} \bullet \left(\frac{BW}{\overline{BW}}\right)^{a}$ *. The shaded area represents AUC values within 1% ± 20% of typical AUC.*

as to the relationship between dosing approaches and α values.

Therapeutic Window

Whether a dosing approach is acceptable also depends on the width of the targeted range of exposure as illustrated in Figure 8. When a drug has a wide therapeutic window, an AUC difference more than ±20% may still be tolerated without additional safety issues. For example, if a 100% AUC difference is acceptable in terms of efficacy and safety, both dosing approaches should work well for mAbs with an α range of 0 to 1.02. However, for mAbs with a narrow therapeutic window, a comprehensive analysis of body size effect on dosing strategy in terms of risk/benefit ratio is necessary.

Contribution of Body Size Effect to Overall Variability in Exposure

In addition to body size, many other factors, as we discussed earlier, may also cause the difference in drug exposure among patients. The contribution of intersubject variability caused by the difference in body size to overall variability also plays a role in determining whether the dose needs to be adjusted based on BW. Table III shows the contribution of body size to the overall intersubject variability of relevant PK parameters for 7 mAbs. When body size only explains a very small percentage of the intersubject variability, for example, in case of bevacizumab and efalizumab, adjusting the dose based on body size would lead to minimal reduction in exposure variability. On the other hand, if body size is a major source for intersubject variability, body size–based dosing may provide a significant benefit when supported by other factors, such as a narrow therapeutic window.

Table III Percentage Contribution of Body Size Measurements to the Overall Intersubject Variability of Pharmacokinetics (PK) Parameters

mAbs	CL	V1
Bevacizumab	2.74	11.1
Trastuzumab	NA	4.6
Pertuzumab	11.9	28.3
Infliximab	NA	15.1
Golimumab	NA	13.6
Efalizumab	2.9	NA
Rituximab	4.81	22.6

Effect of Dosing Approach on PD of the Drug

As the ultimate goal of a clinical study is to achieve its efficacy and safety endpoints, efficacy data, safety data, and surrogate PD markers, when available, supersede PK data. It is well known that intersubject variability in drug response is generally greater than

that in exposure measures because of differences in disease state and genetic variations in drug targets.[17-19] Therefore, the clinical benefit, if any, of body size–based dosing with regard to exposure measurements could be further "diluted" in terms of response or PD measurements as shown in this study for omalizumab (Figure 7). It should be noted that the effect of body size on PD endpoint should be evaluated for each individual mAb under development when data are available.

Relationship Between mAb Type and Body Size Effect on mAb PK

The mAbs investigated in this analysis include 3 chimeric, 8 humanized, and 1 fully human mAbs. Seven of them show linear PK, while nonlinear clearance is involved for 5 of them (Table II). The results of this simulation show that there is no intrinsic correlation between the type of mAb and effect of BW on mAb disposition. Therefore, whether a mAb should be dosed based on body size or with a fixed dose cannot be determined by their type and elimination pathways.

Other Factors

In addition to achieving less variability in PK and PD among patients, different dosing approaches may also have an impact on clinical practice and drug development. Fixed dosing provides numerous advantages over body size–based dosing. It is more convenient for pharmacists or nurses to prepare and administer a unit dose to patients. This has an important safety implication as it could avoid or reduce errors in calculating and preparing an individualized dose for each patient. By administering a unit dose, it could also prevent from wasting leftovers in contrast to individualized dosing based on body size. This is especially important for mAbs because mAb manufacturing is often expensive and time consuming. Therefore, when there is no advantage of one dosing approach over another from a PK and PD perspective, fixed dosing is the approach of choice.

Dosing Approach for Adult FIH and Early Stage Clinical Studies

When an mAb is first tested in humans, the effect of body size on PK and/or PD parameters in humans is unknown. Because no obvious advantage has been identified for one approach over the other in terms of reducing variability in PK/PD measurements, either dosing approach may be used in FIH and other early stage trials before the effect of body size on PK and PD in humans can be evaluated. However, we recommend using fixed dosing approach because it offers advantages in ease of preparation, reduced cost, and reduced chance of dosing errors.

Dosing Approach for Phase 3 Studies in Adult Patients

The intended dosing approach for the to-be-marketed product is preferably selected before the start of the phase 3 studies so that the efficacy and safety of the dosing approach can be evaluated in the phase 3 program to support regulatory approval. Unlike the situation for FIH studies, by the time phase 1 and/or phase 2 studies have been completed, data become available to evaluate the effect of body size on drug exposure, PD, or efficacy and safety. A full population PK and PD analysis should be conducted, including covariate evaluation. If body size is identified as a covariate of PK or PD parameters, population and individual performances of both dosing approaches should be evaluated as described in this article. If fixed dosing is better or 2 dosing approaches are similar, fixed dosing should be used for phase 3 studies. If body size–based dosing provides significantly less variability in PK and PD, further evaluation should be conducted using available safety and efficacy data. The dosing approach that is expected to produce an acceptable safety and efficacy profile may be chosen for the phase 3 studies.

CONCLUSION

Body size–based dosing and fixed dosing have been evaluated for 12 mAbs in terms of their population and individual performances in adult patients. It is demonstrated that the 2 dosing approaches perform similarly across the mAbs investigated, with one approach being better for some mAbs and the alternate approach being better for the other mAbs. For adult FIH studies, either approach may be used. However, we recommend fixed dosing as the preferred approach because it offers advantages in ease of dose preparation, reduced cost, and reduced chance of dosing errors. When sufficient data become available, a full assessment of body size effect on PK and PD should be conducted. The final dosing approach for phase 3 trials in adults should be selected based on the established body size effect on PK and PD, the therapeutic window of the mAbs, along with other factors that may impact the outcome

of the study, benefit to patients, and overall drug development.

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