REVIEW ARTICLE

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Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies

Concepts and Lessons for Drug Development

Diane R. Mould[1] and *Bruce Green*[1,2]

1 Projections Research Inc., Phoenixville, Pennsylvania, USA
2 Model Answers Pty Ltd, Brisbane, Queensland, Australia

Contents

Abstract

Monoclonal antibodies (mAbs) have complex pharmacology; pharmacokinetics and pharmacodynamics depend on mAb structure and target antigen. mAbs targeting soluble antigens often exhibit linear pharmacokinetic behavior, whereas mAbs targeting cell surface antigens frequently exhibit nonlinear behavior due to receptor-mediated clearance. Where nonlinear kinetics exist, clearance can change due to receptor loss following repeated dosing and/or disease severity. mAb pharmacodynamics are often indirect, with delayed clinically relevant outcomes. This behavior provides challenges during clinical development; studies must be carefully planned to account for complexities specific to each agent.

Selection of a starting dose for human studies can be difficult. Species differences in pharmacology need to be considered. Various metrics are available for scaling from animals to humans. Optimal dose selection should ensure uniform mAb exposure across all individuals. Traditional approaches such as flat dosing and variable dosing based upon body surface area or weight should be supported by pharmacokinetic and

pharmacodynamic behavior, including target antigen and concurrent disease states. The use of loading doses or dose adjustments to improve clinical response is also a consideration.

The evaluation of drug interactions requires innovative designs. Due to the pharmacokinetic properties of mAbs, interacting drugs may need to be administered for protracted periods. Consequently, population pharmacokinetic and pharmacodynamic model-based approaches are often implemented to evaluate mAb drug interactions.

This article reviews basic pharmacology of mAbs and discusses the challenge of selecting an initial dose for clinical evaluation, optimal dose regimens, and study designs for drug-drug interaction studies. Material in this article applies equally to endogenous antibodies and therapeutic monoclonal antibodies (mAbs). For clarity, when referring to either, the term 'antibody' is used, and when specifically referring to therapeutic monoclonal antibodies, the term 'mAbs' is used.

There are several antibody classes or isotypes: IgA, IgD, IgE, IgG, and IgM, each with well documented pharmacological properties.[1] The most prevalent isotype is IgG, which constitutes approximately 85% of serum immunoglobulins, with an average concentration of 11–14 g/L in normal adults.[2] Because of its role in humoral protection, the IgG isotype and its derivatives are the primary focus for therapeutic development.

The pharmacokinetics and pharmacodynamics of mAbs and constructs are dependent on structure. Understanding the link between structure and associated function is important to anticipate the pharmacological behavior of these agents. Integration of pharmacokinetic and pharmacodynamic studies during early drug development is critical to the development of appropriate dose regimens and the planning of informative studies.[3] Determining whether a mAb exhibits linear or nonlinear clearance, and whether the clearance is stable or changes over time, is necessary for the determination of safe and efficacious dose regimens. Table I shows a list of the pharmacokinetic properties of several marketed mAbs; approximately half of the mAbs exhibit nonlinear clearance and half exhibit linear clearance.

1. Antibody Structure

IgG antibody monomers are constructed of four polypeptide chains: two heavy chains and two light chains connected by disulfide bonds at the 'hinge' region (figure 1). Antibodies have two domains. The variable, or antigen-binding region (Fab), is specific for the antigen target. This variable region contains three short peptide sequences, known as complementarity determining regions (CDRs) that constitute the antigen binding site.[38] The constant region (Fc) consists of heavy chains.[38] The light chain contains one constant domain: C_L. The heavy chain contains three constant domains: C_H1, C_H2, and C_H3. The latter two domains are involved in interactions between the antibody and various components of the immune system, binding to either the C1q receptor, which activates the complement cascade (CDC), or Fcγ receptors (FcγR) on immune effector cells. Binding to FcγR elicits antibody-dependent cellular cytotoxicity (ADCC).[39] Each heavy chain also has a carbohydrate moiety covalently attached to the C_H2 region, which relates to the antibody's effector function.[40]

2. Antibody Pharmacokinetics

2.1 The Brambell Receptor

In 1965, Spiegelberg and Weigle[41] reported a 10–20 day half-life for the Fc-region fragment, similar to that of an intact antibody half-life of 23 days. Fab fragments are cleared quickly, with a half-life of approximately 0.18 days. This work, together with research reported by Ein and Waldmann[42] suggested that the Fc region was integral to the circulating half-life of antibodies. This finding has also been evaluated in mAbs whose Fc components have been altered to increase Brambell receptor (FcRn) binding affinity, although substantial enhancement of Fc binding affinity has not altered pharmacokinetic behavior.[43]

IgG homeostasis is maintained primarily by recycling or salvage by FcRn,[44,45] which is also involved in transmission of maternal immunity to newborns.[46] Antibodies bound to soluble antigens attach to FcRn and are internalized into cells, where antigen is degraded and intact antibody is returned to the cell surface and released into the circulation. In adults, FcRn is primarily expressed in the vascular endothelial cells or reticuloendothelial system (RES). FcRn is also detectable on monocyte cell surfaces, tissue macrophages and dendritic cells.[47]

FcRn salvage can be saturated at high IgG concentrations. Morrell et al.[48] showed that elevated concentrations of any

Table I. The pharmacokinetics of marketed antibodies and selected dose regimens

Name	Therapeutic area	Type	Pharmacokinetic behavior	Weight on clearance (published)	Weight on clearance (US FDA review)[a]	Dosing	References
Abciximab	Cardiovascular	Fragment	Linear	Linear	No public clinical pharmacology review	mg/kg	4,5
Abatacept	Inflammatory	Fusion protein	Linear	Linear	Unadjusted and adjusted linearly by weight	Stratified by weight	6,7
Adalimumab	Inflammatory	mAb	Linear	None reported	CL increased by 25% over 82 kg bodyweight	Flat dose	8,9
Alefacept	Inflammatory	Fusion protein	Nonlinear		Not discussed	Flat dose	10
Alemtuzumab	Oncology	mAb	Nonlinear	Not identified	Not discussed	Flat dose	11,12
Basiliximab	Transplantation	mAb	Not reported	Not identified	Not significant using 2-stage approach	Flat dose	13
Bevacizumab	Oncology	mAb	Linear	Power function of weight	Power function of 0.368 on weight	mg/kg	14
Cetuximab	Oncology	mAb	Nonlinear	Power function of weight on Vmax	Not significant	mg/m^2	15,16
Daclizumab	Transplantation	mAb	Linear	Power function of weight	Power function of 0.463 on weight	mg/kg	17
Eculizumab	Inflammatory	mAb	Nonlinear		Not significant		18
Efalizumab	Inflammatory	mAb	Nonlinear in early publications Linear from FDA		Power function of 0.754 on weight	mg/kg	19,20
Etanercept	Inflammatory	Fusion protein	Linear	Not identified	Not significant	Flat dose	21
Gemtuzumab	Oncology	mAb/chemotherapeutic conjugate	Company reported linear but clearance decreases over time Nonlinear		Not discussed, reported as having no effect (prescribing information)	mg/m^2	22,23
Golimumab	Inflammatory	mAb	Linear	Power function of 0.778 on weight	Power function of 0.605 on weight	Flat dose	24,25
Ibritumomab tiuxetan	Oncology	mAb	Not reported		No public clinical pharmacology review	MBq/kg	26
Infliximab	Inflammatory	mAb	Linear		Not discussed	mg/kg	27
Muromonab-CD3	Transplantation	mAb	Not reported		No public clinical pharmacology review	Flat dose	28
Natalizumab	Neurology (MS)	mAb	Nonlinear		Not significant	Flat dose	29
Omalizumab	Inflammatory	mAb	Linear		No public clinical pharmacology review but doubling bodyweight doubles CL	By IgE and bodyweight categories	30

Continued next page

Table I. Contd

Name	Therapeutic area	Type	Pharmacokinetic behavior	Weight on clearance (published)	Weight on clearance (US FDA review)[a]	Dosing	References
Palivizumab	Antiviral	mAb	Not reported		No public clinical pharmacology review	mg/kg	31
Panitumumab	Oncology	mAb	Linear + nonlinear		Not significant	mg/kg	32
Ranibizumab	Macular degeneration	mAb	Linear		Not significant. CRCL was included	Flat dose intravitreal	33
Rituximab	Inflammatory	mAb	Linear		No public clinical pharmacology review	mg/m^2	34
Tositumomab	Oncology	mAb	Nonlinear		Not discussed	Flat dose	35
Trastuzumab	Oncology	mAb	Nonlinear		Not significant	mg/kg	36
Ustekinumab	Dermatology	mAb	Linear	Power function of 1.01 on weight	No public clinical pharmacology review	Flat dose	37

a Not significant means weight was evaluated but was not found to be an important predictor of clearance. Not discussed means weight was not considered or discussed in the review or during pharmacokinetic model assessments.

CL = clearance; **CRCL** = creatinine clearance; **mAb** = monoclonal antibody; **MS** = multiple sclerosis; **Vmax** = maximal clearance for the mAb.

IgG subclass substantially shortened the half-life, yielding an inverse relationship between IgG concentration and half-life. In some patients, such as those with multiple myeloma, a high production of IgG antibodies results in a shortened half-life.[49] When a mAb is administered at very high concentrations, such as high-dose intravenous immunoglobin (IVIG), shortened IgG half-life attributed to saturation of the FcRn salvage pathway has been reported.[50] Jin and Balthasar[51] conducted *in vivo* experiments in a murine model, attributing this interaction to FcRn saturation at an IVIG dose of approximately 1 g/kg. Bleeker et al.[52] extrapolated their model to humans and predicted gradually decreasing autoantibody levels after IVIG administration (2 g/kg), with a maximum reduction of approximately 25% after 3–4 weeks of treatment. Endogenous IgG levels would not be expected to affect antibody elimination; similarly, standard therapeutic doses of mAbs,[53] which are usually 0.5–10 mg/kg, are not expected to produce IgG levels that saturate FcRN salvage.

2.1.1 The Fcγ Receptors

There are three other classes of FcγRs, which are expressed by various phagocytic cells, B and T cells, and platelets.[54] IgG antibodies bind FcγRs with various affinities, ranging from low (FcγRII) through medium (FcγRIII) to high (FcγRI).[55] Binding to these receptors elicits CDC or ADCC. Antibody clearance through the RES may be partly regulated through interactions with the different classes of FcγRs. Thus, in addition to their role in pharmacological activity, FcγRs may contribute to the elimination of circulating antibodies. However, mAbs with reduced ability to bind FcγR have not shown substantially altered clearance.[56]

2.1.2 Mechanisms of Monoclonal Antibody (mAb) Clearance

Because of their high molecular weights, antibodies do not undergo renal elimination or metabolism by hepatic enzymes such as cytochrome P450 (CYP).[57] The primary route of antibody clearance is via proteolytic catabolism, which occurs at sites that are in rapid equilibrium with plasma. The exact locations of antibody catabolism have not been identified.[58] mAbs directed against soluble antigens (e.g. cytokines) generally exhibit dose-proportional behavior with linear clearance, presumably because the primary route of clearance is limited to catabolism.[53,57]

Receptor-mediated clearance may also be important.[59] This mechanism was proposed for several mAbs that target antigens expressed on cell surfaces.[19] In addition to proteolysis, binding and internalization of mAb-receptor complexes can result in rapid, saturable clearance routes. In such cases, mAb clearance

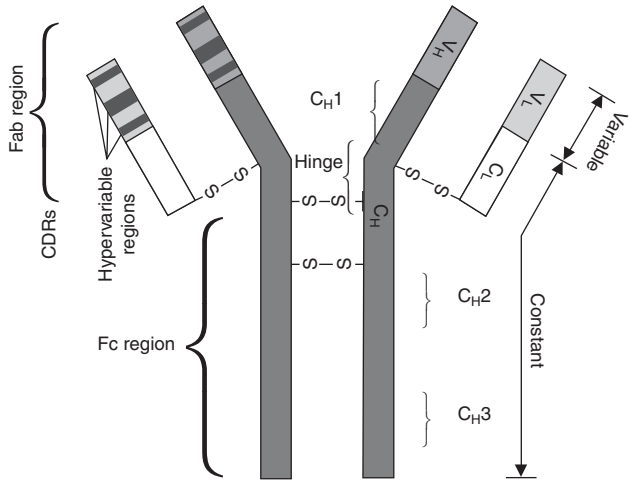

Fig. 1. Generalized structure for a monoclonal antibody monomer. **CDRs** = complementarity determining regions; $\mathbf{C_H}$ = constant heavy chain; $\mathbf{C_L}$ = constant light chain; **Fab** = antigen-binding fragment; **Fc** = constant fragment; **S** = sulfide; $\mathbf{V_H}$ = variable heavy chain ; $\mathbf{V_L}$ = variable light chain.

becomes nonlinear and may show time-dependent changes as receptor density is altered by mAb activity.[11,60] In the case of gemtuzumab, serum concentrations and the terminal half-life increased after the second dose when compared with the first dose. The increased half-life was believed to result from decreased clearance by CD33+ blast cells due to reduced tumor burden following the first dose.[22]

The contribution of receptor-mediated clearance to overall clearance depends on mAb concentrations and distribution, together with target receptor expression, internalization, and turnover rates. Therefore, mAbs can demonstrate schedule dependence,[61] where the apparent activity decreases at higher doses due to saturation of target antigen receptors, thus preventing further pharmacological effect. In some cases, cell surface receptors are 'shed' into the serum, circulating as free antigens. mAbs can bind to shed receptors, resulting in the formation of an antibody-receptor complex that may result in clearance of the mAb, or may have no impact on its clearance other than transiently lowering free mAb concentrations. Thus, mAb pharmacokinetics, especially clearance, can vary depending on the target antigen. Given the two potential primary clearance mechanisms for most therapeutic mAbs, a generic pharmacokinetic model as seen in figure 2 can be proposed. In this model, linear and nonlinear clearances reflect catabolic and receptor-mediated clearance, respectively.

2.1.3 Formation of Neutralizing Antibodies

An additional clearance mechanism is the development of an immune response (e.g. anti-globulin response) to a mAb. An immune response to a mAb can affect the pharmacokinetics by increasing clearance, and/or impairing binding.[62] Anti-globulin responses are classed as neutralizing or non-neutralizing depending on their effect on the activity of the mAb.[57] These responses are designated according to the nature of the mAb construct: human anti-mouse antibodies (HAMA), human anti-chimeric antibodies (HACA), and human anti-human antibodies (HAHA). All therapeutic mAbs approved to date have shown some immunogenicity, even in immunosuppressed patients.[39]

Various factors can contribute to the development of an immune response. Prior exposure and immune response to a structurally similar mAb can predispose a patient to exhibit an immune response. The route of administration can sometimes affect immunogenicity, with the intravenous route of administration usually being the least immunogenic. Generally, the intramuscular and subcutaneous routes are more immunogenic. Post-translational modifications, such as glycosylation, may also present antigenic determinants that can increase immunogenicity. Aggregates in the dosing formulation may enhance immunogenicity.

2.1.4 Covariates Affecting mAb Clearance

When evaluating the pharmacokinetic behavior of a mAb, there are numerous factors that may be predictive of pharmacokinetic variability. For mAbs exhibiting nonlinear clearance,

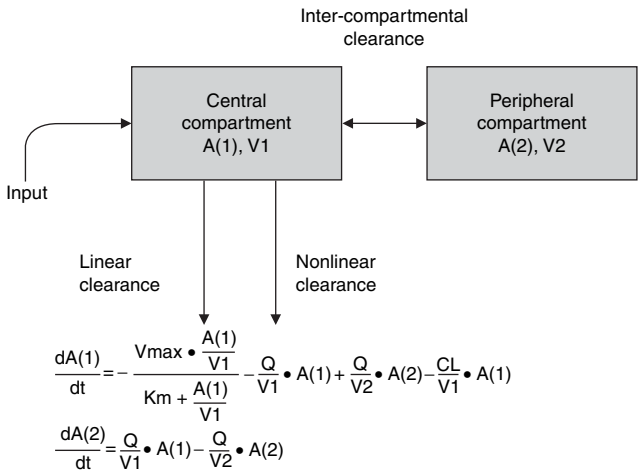

Fig. 2. Generalized pharmacokinetic model for antibody monomer. The boxes represent compartments. The central compartment is representative of the blood or serum and the peripheral compartment is representative of the tissue. In this schematic, monoclonal antibodies (mAbs) can be removed from the blood by either linear or nonlinear mechanisms. **A** = amount; **CL** = clearance; **dA**/**dt** = change in amount per change in time; **Km** = Michaelis constant (e.g. concentration at half maximal clearance); **Q** = inter-compartmental clearance; **V** = volume of distribution; **Vmax** = maximal clearance for the mAb.

cell receptor density or receptor-positive cells should be considered as a potential covariate.[11] This information may be indirectly available in terms of patient status or disease stage, as the receptor density or alternatively the numbers of receptor-positive cells may be correlated with disease severity.[63] Changing to new therapeutic indications, where patients may exhibit different receptor densities, can result in altered mAb clearance, even for mAbs that exhibit linear clearance. For daclizumab, a mAb targeting CD25 receptors on activated T cells, the half-life in patients with graft versus host disease (GvHD) ranged from 79 to 94 hours.[64] When used prophylactically for GvHD, half-life was increased to 165 hours.[65] In renal transplant patients, half-life was reported to be 240 hours.[66] The pharmacokinetics of daclizumab was reported to be linear in all indications, despite the fact that daclizumab targets a cell surface antigen.

Body size, as measured by weight or body surface area, is frequently cited as a predictor of clearance for mAbs,[67] particularly those that exhibit linear clearance, suggesting that larger individuals clear mAbs more rapidly than smaller individuals without compensatory increases in FcRn-mediated salvage. The effects of other demographic factors such as age, sex, and renal or hepatic function on the pharmacokinetics of mAbs are controversial and rarely reported.[68] A population pharmacokinetic evaluation of efalizumab reported a modest effect of age on clearance.[69] The package insert for adalimumab suggests a weak inverse relationship between clearance and patient age. The effect of age may be attributable to decreased liver blood flow in elderly subjects and consequently limited access to the RES. Sex differences in mAb clearance have been reported,[70] but may be due to differences in bodyweight. In cases of hepatic impairment or injury, expression of complement receptors as well as FcγRs may be depressed, altering mAb clearance.[71] Given the high molecular weight of a mAb, renal clearance is not expected.[57] Lastly, concomitant administration of other agents that may affect mAb clearance by competing for binding sites or reducing receptor density must be considered as potentially affecting clearance.

2.2 Distributional Behavior of mAbs

Although mAbs distribute widely within the body, transfer across cell membranes is limited due to their size and hydrophilicity. Karanikas et al.[72] demonstrated that there is little cellular penetration of mAbs, even in cells carrying target receptors. Lin et al.[73] evaluated the distribution of a recombinant humanized IgG1 mAb directed against vascular endothelial growth factor (VEGF) in rabbits. Serum concentrations of the mAb were 10-fold higher than the highest tissue concentration. After 24 hours, evaluable autoradiography was limited due to the recycling of the labeled amino acids by the body. Consequently, mAbs appear to have a distributional volume in the order of 0.1 L/kg, approximately equal to the extracellular fluid volume.

2.3 Absorption

mAbs are administered parenterally, usually via intravenous infusion or subcutaneous injection. Little is known about the mechanism of absorption of mAbs administered via subcutaneous or intramuscular injection, although uptake is primarily via the lymphatic system.[74,75] mAb absorption from the subcutaneous route is slow, with peak concentrations occurring approximately 6–9 days after administration. When administered subcutaneously or intramuscularly, the bioavailability of mAb is variable. Because the fraction absorbed (bioavailable fraction) is dependent on the molecular weight of the protein,[76] bioavailability of most mAbs ranges from 40% to 80%.

2.4 Pharmacodynamics

As mentioned previously (section 2.1.2), mAbs can be targeted against soluble antigens or against antigens on cell surfaces. Regardless, the pharmacodynamic behavior of mAbs is commonly described using modifications of the standard indirect effect models.[77]

For mAbs that target soluble antigens, binding and subsequent formation of the mAb-antigen complex reduces the circulating antigen, preventing the antigen from acting. Antigen loss can ameliorate symptoms arising from its presence. In such cases, the free mAb concentration is considered to inhibit the action of the antigen.

For mAbs targeting cell surface antigens, there are two types of pharmacological activity, lytic or coating. For lytic activity, mAb binds to the cell surface receptor and stimulates loss of the receptor-positive cells via ADCC or CDC; a schematic is presented in figure 3a. For coating activity, mAb binding to target antigen is 'nonproductive', resulting in a stimulation of receptor loss. Alternatively, when mAb binds to the antigen, it results in steric blockage of the receptor as shown in figure 3b.

The pharmacodynamic activity of mAbs targeted against cell surface antigens can be evaluated via fluorescence activated cell sorting (FACS). FACS can determine the population of cells expressing the receptor and the fraction of cell surface receptors bound by the mAb. Because changes in receptor density can be followed using this method, more mechanistic models have been proposed.[79] In these models, the relationship between mAb

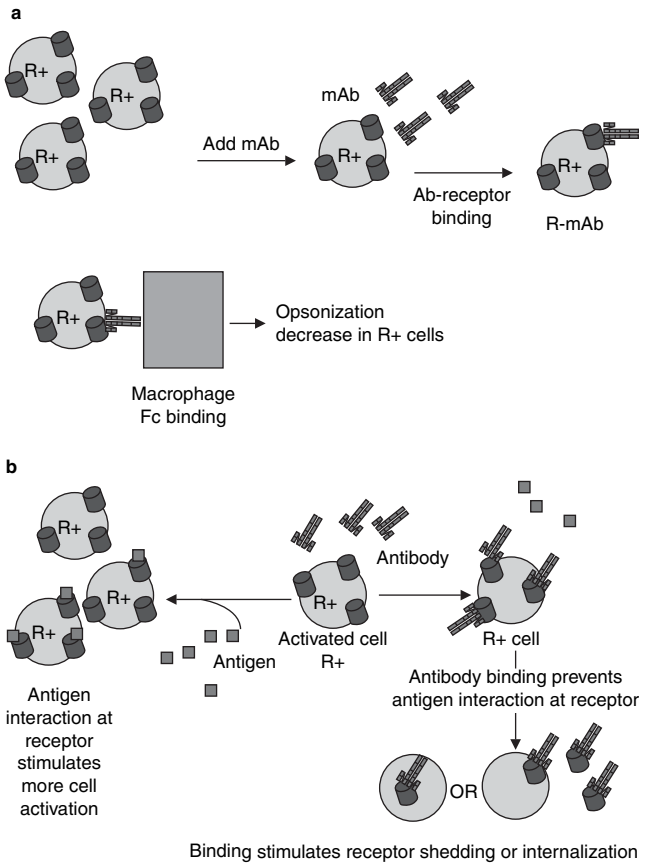

Fig. 3. General schematic diagrams for monoclonal antibodies (mAbs) targeted against cell surface receptors (R). (**a**) Represents lytic activity where the constant fragment (Fc) portion of the mAb induces antibody-dependent cellular cytotoxicity or the complement cascade. (**b**) Represents coating activity where the antibody blocks the target antigen, resulting in one of the following: (i) prevention of a productive interaction; (ii) internalization and loss of target antigen; or (iii) increased shedding, resulting in reduced receptor positive cells.

concentration and bound receptors can be explicitly described and the bound mAb-antigen complex is used to drive a modified indirect effect pharmacodynamic model.

Study designs to elucidate the pharmacodynamic behavior of mAbs should incorporate several dose levels. Varying rates and durations of drug input can help distinguish between stimulatory or inhibitory behavior.[80] If the mAb targets receptor-positive cells, such studies may need to be conducted in patients, and population-based modeling approaches may be necessary.

3. Dose Selection

3.1 Selecting an Initial Dose

An early challenge during mAb development is the selection of a safe starting dose for first-time-in-human (FTIH) studies. When selecting this dose, the risk of adverse immune-mediated drug reactions, such as cytokine storm, autoimmunity, immunogenicity, and immunosuppression, must be evaluated. The evaluation of nonclinical data must take into account differences between primate and human immune systems, the species evaluated and preclinical study design limitations.[81] Species differences between target ligands may produce pharmacokinetic or pharmacodynamic differences. Unexpected and serious events have occurred when administering mAbs, such as the onset of progressive multifocal leukoencephalopathy (PML) observed with natalizumab, reactivation of Epstein-Barr virus (EBV) with anti-CD3, and the occurrence of cytokine storm with an anti-CD28 superagonist.[82]

The US FDA produced a guidance document on dose selection for the minimum recommended dose for FTIH studies[83] that suggests selection of initial doses based on bodyweight (e.g. mg/kg) in order to scale exposure seen in nonclinical studies to safe levels in humans. This document is not specifically aimed at providing guidance for dose selection of mAbs.

While many mAbs exhibiting linear pharmacokinetics have been reported with bodyweight as a covariate, it is generally not a linear relationship. This suggests that dose adjustment metrics such as lean bodyweight (LBW)[84] or body surface area (BSA) could be potentially more suitable to reduce the between-subject variability in exposure. In cases where linear pharmacokinetic behavior is expected, the allometric model[85] may be applicable; however, if nonlinear pharmacokinetic behavior is expected, the use of this scaling function may be inappropriate, as receptor density does not always increase with body size. In addition, special consideration should be given to dose adjustments in obese individuals.[86] Table I shows a listing of the reported pharmacokinetics and the effect of bodyweight on clearance for many marketed mAbs. In this table, only three of the 26 mAbs listed were found to have clearance that varied linearly with bodyweight.

Care should be taken when selecting initial doses for antibodies that are targeted against cell surface receptors, as nonlinearity may not be evident in animal models due to poor specificity of the human mAb for the animal receptor.[78] In figure 4a, the pharmacokinetics of efalizumab in humans are shown as nonlinear due to receptor-mediated clearance. This receptor-mediated clearance does not occur in rabbits; therefore, the pharmacokinetic profile of efalizumab in this animal species is linear (figure 4b). When nonlinear clearance is expected, data from animal models expressing receptors with good affinity for the mAb are important to predict human pharmacokinetic behavior. An alternative approach is to develop mAb analogues specific for the animal model. This latter approach provides additional benefits, in that the formation of

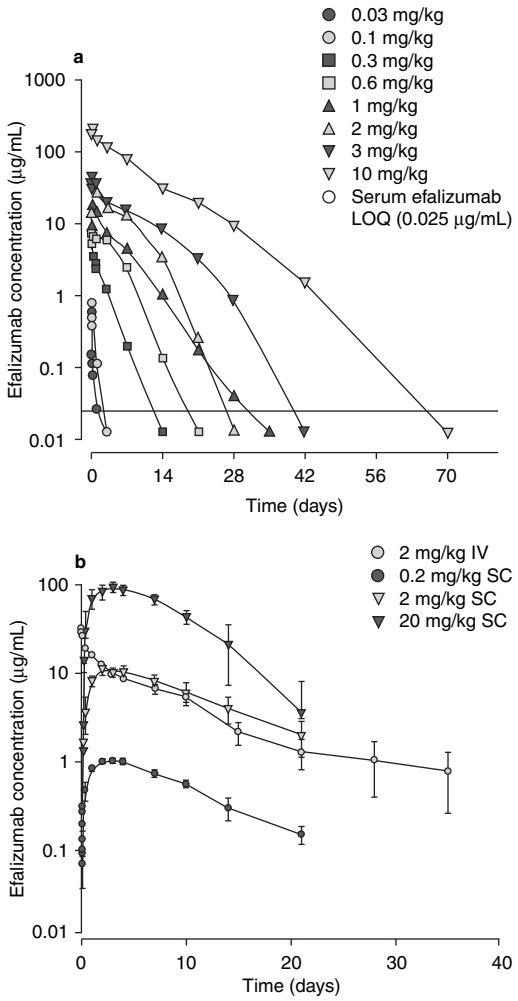

Fig. 4. Inter-species differences in pharmacokinetics when receptor-mediated clearance is evident.[78] Mean concentration-time profiles of efalizumab administered intravenously (IV) or subcutaneously (SC) to (**a**) humans or (**b**) rabbits. The nonlinear behavior of efalizumab in humans is evident, while in rabbits the pharmacokinetics are linear. **LOQ** = limit of quantitation.

neutralizing antibodies in the animal model is generally less problematic, and antibody salvage will also be effective.

Modeling and simulation are useful to help select a safe and efficacious initial dose regimen.[6] An example of this is the use of modeling and simulation to guide the selection of dosing of ABX 10241, a mAb targeting parathyroid hormone (PTH).[87] In this example, allometric scaling worked well to predict human pharmacokinetics. The FDA guidance document supports the application of modeling[83] for initial dose selection: ''Modeling can be used with greatest validity to estimate human starting doses in special cases where few underlying assumptions would be necessary. Such cases are exemplified by large molecular weight proteins (e.g. humanized mAbs) that are intravenously administered, are removed from circulation by endocytosis rather than metabolism, have immediate and detectable effects on blood cells, and have a volume of distribution limited to the plasma volume. In these cases, allometric, pharmacokinetic, and pharmacodynamic models have been useful in identifying the human mg/kg dose that would be predicted to correlate with safe drug plasma levels in nonhuman primates. Even in these cases, uncertainties (such as differences between human and animal receptor sensitivity or density) have been shown to affect human pharmacologic or toxicologic outcomes, and the use of safety factors as described in [the] guidance is still warranted.''

3.2 Selection of a Dose Regimen

Dose selection should be supported by the observed pharmacokinetic behavior for that mAb; inappropriate dose regimens can increase variability. It is important to minimize variability in patient exposure in order to ensure that subjects are not under-dosed, which can lead to treatment failure, and are not exposed to excessively high mAb concentrations, which can lead to greater (or longer) than desired pharmacodynamic responses and potentially to adverse events. There are several potential dose regimens that can be employed for mAbs: (i) a flat dose, where subjects all receive the same dose; (ii) an individualized dose, which usually involves a bodyweight or BSA-based dose; and (iii) a Bayesian individualized dose, where the dose is adjusted using a nomogram or the subject's individual concentration or response measurement.

An example is provided to illustrate potential differences in exposure for flat and individualized dose regimens. Table II shows the area under the concentration-time curve (AUC) for two hypothetical mAbs (drug X and Y), which were administered subcutaneously using both the flat and individualized dose regimens. The pharmacokinetic parameters used for the simulations are also shown in table II, with concentration-time profiles provided in figure 5. For drug X, where weight was not an important predictor of clearance, a flat dose provides a uniform drug exposure (AUC = 83.6 mg • day/L) seen by a single curve in figure 5a. When weight-based dosing was considered for drug X, AUC for heavier subjects increased, as drug clearance was independent of weight (figure 5b). Conversely, for drug Y where weight does affect clearance, AUC decreased with weight when a flat dose was used (figure 5c) and can be 'normalized' by giving a weight-based (e.g. 0.5 mg/kg) dose (figure 5d). These simulations demonstrate that between-subject variability in drug exposure can be increased if an inappropriate dosing metric is used, or reduced if dosing reflects the pharmacokinetic properties of the drug. Wang et al.[88] compared flat dosing to body size-based dosing for several approved mAbs. This work suggests that the choice between a flat

Table II. Model parameters and exposure for weight-based simulations

Drug	Dose	Pharmacokinetic parameters	AUC by weight (mg • day/L)			
			50 kg	80 kg	110 kg	140 kg
X	45 mg Flat dose	CL/F = 0.465 L/day V/F = 15.7 L Ka/F = 0.354/day	83.6			
	0.5 mg/kg		46.4	74.3	102	158
Y	45 mg Flat dose	CL/F = 0.465*(WT/90)^0.84 L/day V/F = 15.7*(WT/90)^0.807 L Ka/F = 0.354/day	136	92.1	70.7	57.9
	0.5 mg/kg		75.6	81.9	86.5	90.1

AUC = area under the concentration-time curve; **CL** = clearance; **F** = relative bioavailability; **Ka** = absorption rate constant; **V** = volume of distribution.

or body size-based dose is dependent on the pharmacokinetic behavior of each mAb and the pharmacokinetic variability. In table I, the pharmacokinetics and dose recommendations are not always consistent. In some cases, doses are based on weight (e.g. the recommended dose is given on a mg/kg basis) with no apparent effect of bodyweight on clearance.

Variability in patient exposure can adversely impact on mAb safety and efficacy. For rituximab, patient exposure is variable even when administered using the same dose[89] and clinical response has been related to rituximab concentrations.[90] Limited information is available about demographic factors affecting pharmacokinetic variability, and a better understanding of which factors affect variability is necessary to improve the current dose regimen.

Once pharmacokinetic and pharmacodynamic information is available in humans, model-based evaluations can play a role in determining the appropriate dose regimen and dose adjustments. The dose regimen should minimize variability in patient exposure to achieve a reliable pharmacodynamic response (e.g. maximize receptor saturation) in all patients. For abatacept,[91] modeling and simulation demonstrated that the recommended weight-stratified dosing provided uniform exposure for patients with rheumatoid arthritis. Under this stratified dose regimen, drug exposure was consistent. Additional pharmacodynamic modeling and simulation work showed the selected dose provided maximum reduction in IL-6, leading to a reliable clinical response. Modeling and simulation played a similarly important role in dose selection for efalizumab,[92] supporting both the weight-based dosing and the selected dose regimen.

Based on the pharmacokinetic and pharmacodynamic behavior of a mAb, loading doses may be relevant. In some cases, receptor-positive cells decrease following initial doses, reducing mAb clearance.[22] The mAb dose may then be decreased without compromising patient exposure and response. In other cases, time to achieve target mAb concentrations can be more rapid with the use of loading doses, shortening time to response and improving clinical activity.[93]

4. Drug Interactions

4.1 Pharmacokinetic Drug Interactions

Understanding potential drug-drug interactions (DDI) between new and existing chemical and food entities is an important aspect of the drug development process. DDI studies

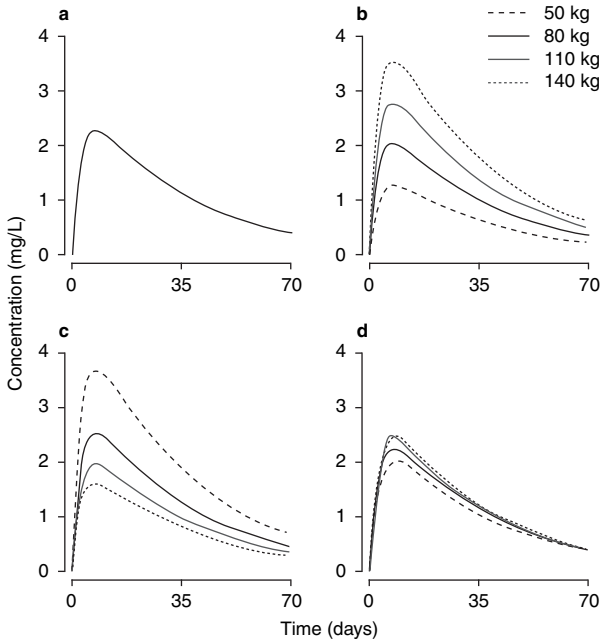

Fig. 5. Simulated concentration-time profiles for subjects of varying bodyweights dosed using a flat dose regimen of 45 mg ([**a**] and [**c**]), vs a 0.5 mg/kg dose regimen ([**b**] and [**d**]). (**a**) and (**b**) apply to a monoclonal antibody (mAb) [drug X] where bodyweight does not affect clearance and (**c**) and (**d**) apply to a mAb (drug Y) where bodyweight does affect clearance.

ascertain if dose adjustments may be required during concomitant administration of an interacting agent. Some drug interactions are now used intentionally in routine clinical practice, such as the coadministration of ritonavir to increase plasma concentrations of lopinavir. However, most DDI studies are designed to assess potential interactions between drugs that are cleared quickly, relative to mAbs.

The FDA has produced a draft guidance document entitled *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*.[94] This document was prepared by the Drug-Drug Interaction Working Group in the Clinical Pharmacology Section of Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research, with input from the Center for Biologics Evaluation and Research. The guidance states that dose selection should "maximize the possibility of finding an interaction and the maximum planned or approved dose with the shortest dosing interval should be used …. Not every drug-drug interaction is metabolism-based, but may arise from changes in pharmacokinetics caused by absorption, distribution and excretion interactions." The guidance indicates that negative findings from *in vitro* and early clinical studies can eliminate the need for later clinical investigations, although this does not often apply to mAbs as interactions can be substantially delayed. Furthermore, there are few animal or *in vitro* models available to screen for likely drug interaction mechanisms for mAbs.

DDIs are broadly classified as either metabolism- or transporter-based. Conventional transporter-based DDIs would not be expected to occur with mAbs, as they are not administered orally. Metabolic interactions are possible, both on chemical entities and on the mAb. Potential DDIs for mAbs are not easily identified, partly due to the nature of mAb-specific clearance mechanisms, together with the pharmacokinetic properties of many mAbs such as the long half-life. DDI studies for mAbs have been summarized in three recent reviews.[95-97] Few formal DDI studies have been performed for mAbs, and DDIs are not always screened during population pharmacokinetic evaluations. One reason for this is that, until recently, mAb safety was generally accepted.[98]

4.1.1 Effects of mAbs on Chemical Entities

Effects of mAbs on chemical entities are rarely reported. mAb-induced changes in cytokine levels, however, can result in downregulation of mRNA and decreased CYP expression.[99] Cytokines have different potencies to decrease CYP expression and different CYPs appear to be regulated by different cytokines via different mechanisms.[100] Basiliximab was reported to increase concentrations of cyclosporine,[101] possibly due to interleukin-2 receptor-mediated alterations of the CYP system, which is also thought to account for the effect of muromonab-CD3 on cyclosporine.[102] An interaction was reported between basiliximab and tacrolimus,[103] possibly due to the same mechanism (cytokine-induced inhibition of CYP3A4). mAbs targeting soluble antigens, which are often cytokines, would therefore be most likely to cause DDIs with chemical agents. Studies assessing the impact of the coadministration of a mAb on the pharmacokinetics of a small molecule are relatively straightforward, although crossover designs will generally not work due to mAb pharmacokinetics.

4.1.2 Effect of Chemical Entities on mAbs

Effects of chemical entities on mAb pharmacokinetics are expected given our present understanding of mAb clearance mechanisms, which involve proteolytic catabolism, salvage by FcRn, and receptor-mediated clearance. Tabrizi et al.[53] suggested that some reported interactions between mAbs and coadministered small-molecule agents may be attributable to modulation of the activity between the mAb and FcγR, or to the effects of the small-molecule drug on the level of FcγR expression. For example, methotrexate was reported to alter the expression of FcγRI on monocytes.[104] Agents that affect any of these routes of clearance must be considered as having a potential impact on mAb clearance, such as has been reported in the package insert, for the interaction between adalimumab and methotrexate. Agents that alter the expression of receptor-bearing cells, or the receptors themselves, may affect mAb clearance, especially if the mAb targets cell surface antigens. Interactions of this nature, such as the effect of mycophenolate mofetil on basiliximab,[105] have been reported. Data from clinical trials where trastuzumab and paclitaxel were administered concurrently reported that trastuzumab concentrations were elevated by 1.5-fold.[106] In this setting, the concomitant medication is an antineoplastic agent, which can reduce tumor burden. Trastuzumab targets human epidermal growth factor receptor-2 (HER2), and exhibits nonlinear clearance on initial dosing. Although the mechanism of clearance for this mAb is not defined, it is possible that the interaction observed is due to a decrease in receptor-mediated clearance.

A risk-based strategy for the assessment of potential DDIs during mAb development has recently been proposed by Zhou and Davis[97] stipulating that the mAb target site should be identified in order to assess the likelihood of DDIs. This would affect mAbs that target cell surface antigens, as other agents can reduce cell count or reduce receptor expression. Another consideration in the risk potential is the therapeutic index of the mAb. mAbs that exhibit toxicity at high doses should be

carefully screened, as should an agent that requires specific concentrations for activity ('coverage'). Zhu et al.[37] reported the application of population pharmacokinetic modeling, which was used in the development of ustekinumab and stratification of the DDI risk potential.[97]

4.2 Drug Interaction Study Designs

Conventional drug interaction studies investigating concomitant drug effects on mAb pharmacokinetics pose definite challenges, as crossover studies with adequate washout periods are not feasible. Most conventional DDI studies are conducted over short periods of time, which is inappropriate for mAbs because of the long half-lives involved. Given the complexities of mAb clearance pharmacology, study designs should be assessed to determine their ability to identify potential interactions.

Simulated scenarios highlight some issues in designing DDI studies for mAbs. The first scenario involves receptor-mediated clearance such as is seen with alemtuzumab.[11] In this case, clearance was nonlinear where Vmax was a function of white blood cell (WBC) count:

$$\text{Clearance} = \frac{\text{Vmax} \bullet \text{concentration}}{\text{Km} + \text{concentration}}$$

$$\text{Vmax} = \text{Vmax}_0 \left(\frac{\text{WBC}}{10 \times 10^9/\text{L}} \right)^{\text{WBC\_Factor}}$$

Vmax is the maximal clearance for the mAb, Km is the concentration at half maximal clearance, and Vmax_0 and WBC_Factor are scale factors relating WBC to Vmax.

It is expected that a coadministered drug, which decreases WBC, could potentially decrease Vmax resulting in decreased clearance and higher associated mAb concentrations. Examples of this type of interacting agent include chemotherapeutic agents and corticosteroids.

To demonstrate the importance of mAb DDI study designs, three simulation scenarios were evaluated. Concentrations and the resultant AUCs were computed for two hypothetical drugs: drug X (as previously shown in table II and figure 5) and drug Z, which featured a receptor-mediated clearance similar to alemtuzumab. The parameters for drugs X and Z together with AUC values for the three simulation scenarios are shown in table III. The three simulation scenarios were:

1. increasing or decreasing clearance as a function of DDI potency;
2. fixing the DDI potency to 1.2 (i.e. a 20% increase in clearance) and evaluating different durations of exposure to the interacting drug;
3. as for scenario 2 but fixing the DDI potency to 2 (i.e. a 100% increase in clearance).

The concentration-time profiles arising under these three simulation scenarios are shown in figure 6.

When the mAb is in the presence of an interacting drug that decreases CL by half, the AUC increases from 83.6 mg • day/L to 122 mg • day/L. Conversely when the interacting drug increases CL by 1.2, 2, and 4 times, the mAb AUC decreases to 73.3, 47.7, and 24.4 mg • day/L, respectively (table III). These results are deceptively encouraging because the initial simulation was constructed under the premise that the interacting drug was present for the entire time the mAb was measurable (i.e. 70 days). In the middle panels of figure 6, linear and nonlinear clearance values were increased by 20% in the presence of the interacting drug, as this is the critical value deemed to be clinically relevant in the FDA guidance document. The interacting drug was

Table III. Model parameters and exposure for drug-drug interaction (DDI) simulations

Drug	Dose	Pharmacokinetic parameters	AUC (mg • day/L)														
			by DDI potency (panel A of figure 6)					by DDI duration, DDI potency = 1.2× (panel B of figure 6)					by DDI duration, DDI potency = 2× (panel C of figure 6)				
			0.5×	No DDI[a]	1.2	2	4	0[a]	1 wk	2 wk	4 wk	8 wk	0[a]	1 wk	2 wk	4 wk	8 wk
X	45 mg flat dose	CL/F = 0.465 L/day V/F = 15.7 L Ka/F = 0.354/day	122	83.6	73.3	47.7	24.4	83.6	81.6	79.2	75.9	73.6	83.6	74.3	64.1	53.2	48.0
Z	7.5 mg flat dose	Vmax = 0.5 mg/day Km = 0.3 mg/L V = 10 L Ka/F = 0.354/day	189	92.1	75.3	42.1	17.9	92.4	85.5	79.9	76.2	75.8	92.4	62.3	45.9	42.2	42.1

a Reference subject with no DDI.

AUC = area under the concentration-time curve; **CL** = clearance; **F** = relative bioavailability; **Ka** = absorption rate constant; **Km** = Michaelis constant; **V** = volume of distribution; **Vmax** = maximal clearance for the drug.

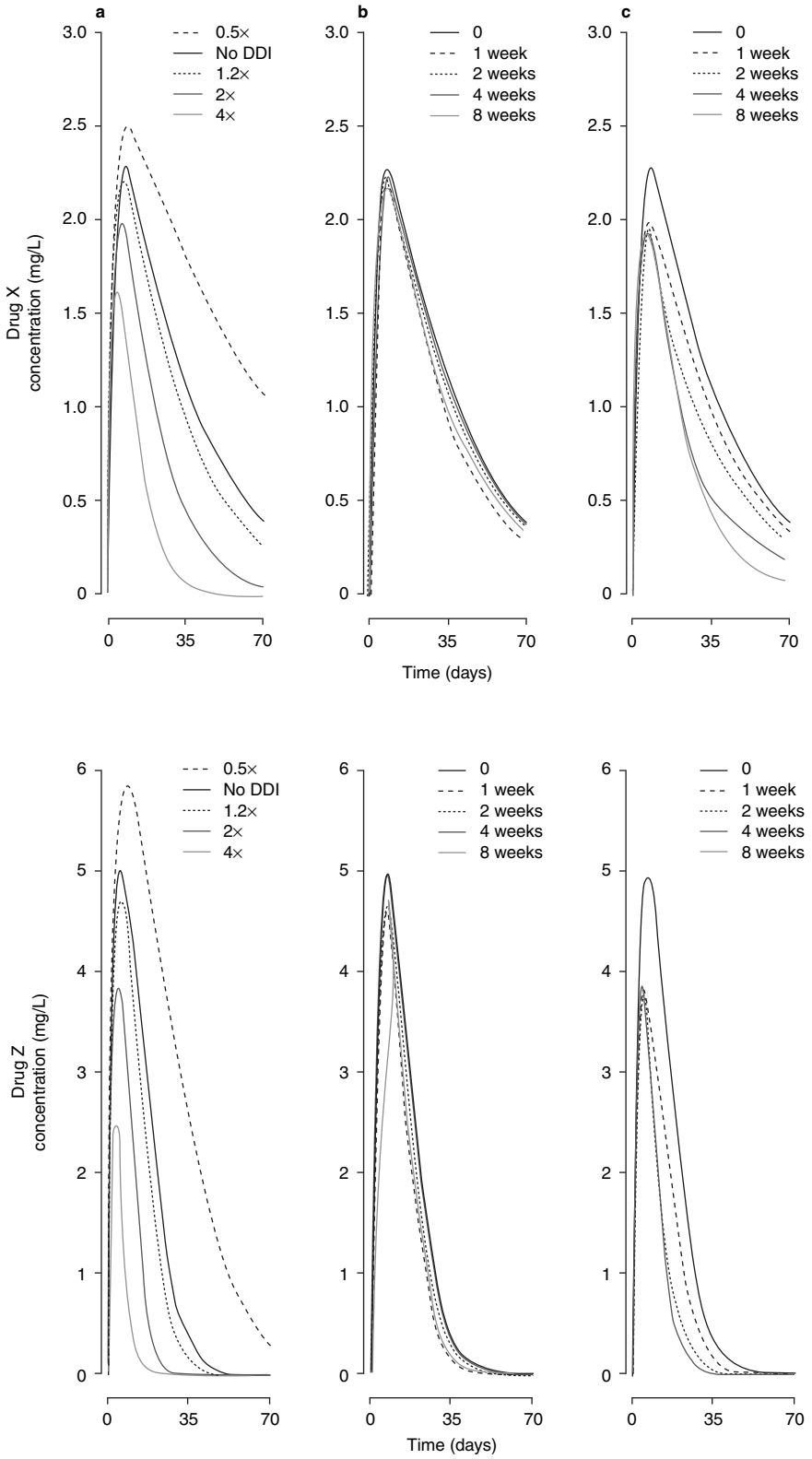

Fig. 6. Simulated concentration-time profiles for subjects with varying drug-drug interaction (DDI) scenarios. (**a**) shows how exposure varies when clearance is either decreased or increased by varying amounts for a monoclonal antibody (mAb) with linear (drug X) and nonlinear clearance (drug Z). (**b**) and (**c**) show how exposure varies when clearance is increased 1.2 or 2.0 times, respectively, for different durations (0–8 weeks) of exposure to an interacting drug. The top row of figures applies to a mAb (drug X) with linear clearance and the bottom row of figures applies to a mAb (drug Z) with nonlinear clearance.

administered from 0 to 8 weeks. Changes in AUC values for relatively short exposure to the interacting drug are less pronounced with short exposures (e.g. 2 weeks or less) and only become notable with protracted exposure to the interacting agent (e.g. 8 weeks). This suggests that the interacting drug needs to be present for at least 8 weeks to show an approximately 20% reduction in AUC for weak pharmacokinetic interactions, although a shorter duration can identify a strong pharmacokinetic DDI.

Because the interacting drug must be present for long periods of time in order to adequately assess a DDI on mAb pharmacokinetics, traditional DDI studies often will show no effect. Therefore, population pharmacokinetic modeling is useful to evaluate DDI assessments with mAbs. Late-phase clinical trials are conducted with a large number of patients who may be administered a variety of concomitant treatments for their disease. Because the concomitant treatments are administered for the entire duration of the study, and study durations often range from weeks to months, the effect of concomitant medications on mAb pharmacokinetics can be evaluated as a covariate, which compares pharmacokinetic behavior to that of subjects not taking the medication of interest.

4.3 Pharmacodynamic Drug Interactions

In some reported pharmacokinetic DDIs, the mechanism may be due to an interacting drug reducing the number of receptors, or reducing receptor-bearing cells, thus affecting receptor-mediated clearance. However, mAbs can also elicit pharmacodynamic interactions where synergistic effects occur when mAbs are concomitantly administered with chemical agents.[95] The taxanes and trastuzumab possess significant clinical activity in metastatic breast cancer. Preclinical testing of trastuzumab combinations with paclitaxel and docetaxel demonstrated additive and synergistic interactions, respectively.[107] The mechanism of this synergistic interaction was investigated by Henson et al.,[108] who found that trastuzumab administered in combination with standard chemotherapy yields a synergistically apoptotic response in breast tumors by reducing anti-apoptotic Mcl-1protein levels.

The use of pharmacodynamic interactions for improving the efficacy of chemotherapeutic agents is growing. For example, the efficacy of intraperitoneal chemotherapy for ovarian cancers is limited by poor penetration of the drug into tumor cells due to rapid drug removal via tumor blood flow. Shah et al.[109] hypothesized that coadministration of anti-angiogenic mAbs (e.g. anti-VEGF) could inhibit drug removal, thereby enhancing efficacy. Pharmacokinetic modeling was conducted to simulate the effect of tumor blood flow on tumor topotecan concentrations. The simulations predicted that tumor blood flow reductions achieved by concomitant administration of anti-VEGF, would lead to substantial increases in tumor topotecan concentrations after intraperitoneal chemotherapy, but would lead to a slight decrease after systemic chemotherapy. *In vivo* experiments conducted using an A2780 xenograft tumor model showed that animals receiving combined intraperitoneal topotecan and an anti-VEGF mAb had approximately 6.5-fold higher tumor topotecan concentrations compared with animals receiving intraperitoneal topotecan alone.[109]

Pharmacodynamic interactions with other antibodies are also being evaluated. Combination therapy with an oral taxane, BMS 275183, and cetuximab was found to exhibit enhanced therapeutic benefit in preclinical tumor models.[110] Inoue et al.[111] described the combined use of paclitaxel with cetuximab in a transitional cell bladder carcinoma in nude mice. Combination therapy resulted in greater regression of tumors compared with either agent alone. They concluded that therapy with paclitaxel increased the ability of cetuximab to inhibit tumorigenicity and metastases, possibly through inhibition of angiogenesis and the induction of apoptosis. Synergy between cetuximab and gefitinib, a tyrosine kinase inhibitor, has also been reported in preclinical studies across a variety of human cancer cell models.[112] These results suggest that cetuximab augments signaling inhibition by gefitinib *in vitro* and that, despite targeting the same receptor, cetuximab and gefitinib have non-overlapping mechanisms of action. Coadministration increases inhibition of cell proliferation, epithelial growth factor receptor (EGFR)-dependent signaling and increases apoptosis. Clinically, the combination of irinotecan and cetuximab in irinotecan-refractory EGFR-expressing metastatic colorectal cancer patients was found to be effective.[113,114]

Designs for studies investigating pharmacodynamic interactions (or potentiation) of drug effects are dependent on the indication, route of administration and timing of administration of these agents. Modeling and simulation can provide insights into regimens that take advantage of mechanistic properties of both agents. Although the development of mechanistic models describing pharmacodynamic interactions between mAbs and small molecules is still nascent, this area of research is growing and has provided some elegant dose regimens.[109]

5. Conclusions

The pharmacokinetics and pharmacodynamics of therapeutic mAbs are often complex, being dependent on both the structure of the antibody and the specific antigen being targeted. The structure and integrity of the Fc portion of the mAb

is important for antibody functionality (e.g. CDC and ADCC) and antibody salvage, yielding the 3- to 4-week half-life reported for many mAbs.

mAbs directed against cell surface antigens often exhibit nonlinear pharmacokinetic behavior, while mAbs directed against soluble antigens often exhibit linear behavior. For mAbs exhibiting nonlinear pharmacokinetic behavior, there are numerous factors that can influence the pharmacokinetics, including receptor density changes over time, receptor shedding, the indication and disease status, and the physiology of the system being targeted. For mAbs exhibiting linear behavior, bodyweight is often reported as being an influential factor in clearance.

With variable clearance, the selection of a safe and efficacious dose regimen is important. Dose regimens should be selected to minimize between-subject variability and provide adequate coverage (e.g. sufficient mAb concentration to elicit a desired clinical response). Selection of dose adjustment metrics should be justified by pharmacokinetic/pharmacodynamic behavior to minimize between-subject variability in exposure and response. It is interesting to note that the use of either Bayesian individualized dosing, or a loading dose and maintenance dose regimen, which would be potentially useful for agents such as gemtuzumab, that exhibit time dependent changes in pharmacokinetic behavior, have not been recommended.

The evaluation of DDIs, whether pharmacokinetic or pharmacodynamic in nature, is also important. Although the clearance of mAbs is different from clearance seen with small molecules, pharmacokinetic interactions for mAbs have been reported. However, the long half-lives of mAbs make traditional study designs difficult to implement. The interacting agent must be present long enough to identify the interaction. Because of the mAb half-life, exposure to the interacting agent may need to be weeks or months. For the same reason, crossover studies with washout periods are usually not feasible. Pharmacodynamic interactions with synergy or potentiation of drug effects when mAbs and small-molecule drugs are coadministered have been reported. These interactions are important to anticipate and study, as they can provide increased benefit to the patient.

Because mAbs are engineered to target specific human antigens, translating data from nonclinical studies into humans is not straightforward. The importance of understanding the pharmacology of mAbs is exemplified by the tragic problems that occurred with TGN 1412[115,116] and the occurrence of PML in subjects treated with natalizumab.[117] Model-based evaluations and simulations are useful tools to explore study designs and understand the behavior of mAbs in the target population.

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Correspondence: Dr *Diane R. Mould*, Projections Research Inc., 535 Springview Lane, Phoenixville, PA 19460, USA.
E-mail: drmould@pri-home.net