Monoclonal Antibody Pharmacokinetics and Pharmacodynamics

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More than 20 monoclonal antibodies have been approved as therapeutic drugs by the US Food and Drug Administration, and it is quite likely that the number of approved antibodies will double in the next 7–10 years. Antibody drugs show several desirable characteristics, including good solubility and stability, long persistence in the body, high selectivity and specificity, and low risk for bioconversion to toxic metabolites. However, many antibody drugs demonstrate attributes that complicate drug development, including very poor oral bioavailability, incomplete absorption following intramuscular or subcutaneous administration, nonlinear distribution, and nonlinear elimination. In addition, antibody administration often leads to an endogenous antibody response, which may alter the pharmacokinetics and efficacy of the therapeutic antibody. Antibodies have been developed for a wide range of disease conditions, with effects produced through a complex array of mechanisms. This article attempts to provide a brief overview of the main determinants of antibody pharmacokinetics and pharmacodynamics.

INTRODUCTION

Antibodies, which are also called immunoglobulins (Igs), are large proteins used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. All Ig molecules are composed of a basic unit of two identical heavy chains and two identical light chains, held together by a number of disulfide bonds. In humans, there are two types of light chains (κ and λ) and five types of Ig heavy chains (α, δ, ε, γ, and μ).[1] Igs are grouped into five classes according to the structure of their heavy chains: IgA, IgD, IgE, IgG, and IgM. Among these, IgG is the predominant class, comprising ~80% of the Igs in human serum. All of the approved therapeutic antibodies are IgGs, and this review focuses on this class.

Intact IgGs have a molecular weight of ~150 kDa and a valence of 2 (meaning that each molecule of IgG contains two identical antigen-binding domains). The antigen-binding sites are located in the complementarity determining regions (CDRs) within the Fab portion of the antibody (**Figure 1**). Fab, which refers to the fragment of antigen binding, is composed of domains associated with the light chain (VL, CL) and domains associated with the heavy chain (VH, CH1). The stem, or Fc, portion of IgG contains the CH2 and CH3 domains of the heavy chains, and this region of the antibody is involved with binding to a wide range of cell-associated receptors (i.e., Fc receptors). The IgG family of antibodies may be further divided, again based on the structure of their heavy chains, into four subclasses: IgG1, IgG2, IgG3, and IgG4. Structural differences among IgG heavy chains lead to differences in subclass binding to Fc receptors and, consequently, to subclass-specific differences in processes mediated by Fc receptors (e.g., activation of complement or antibody-dependent cell-mediated cytotoxicity). For example, antibody-dependent cell-mediated cytotoxicity by mononuclear cells is more efficient for IgG1 and IgG3 than for IgG2 and IgG4. On the other hand, IgG4 is much more active in recruiting the alternative complement pathway than are the other three IgG subclasses.[1]

Antibody drugs typically possess several desirable pharmacological characteristics, such as long serum half-lives, high potency, and limited off-target toxicity. Initial antibody therapies were prepared from hyperimmune sera, collected following immunization of animals. The resulting antibody product, which is derived from a large number of genetically distinct cells, contains a distribution of Ig isotypes and affinities. In 1975, Köhler and Milstein demonstrated that antibody-producing B lymphocytes may be fused with myeloma cells to generate hybrid cells (hybridomas) that propagate indefinitely in culture and secrete antibody.[2] Cloning the hybridoma cells enabled efficient production of antibody derived from a single progenitor, and the resulting monoclonal antibody (mAb) preparations are

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ANTIBODY ABSORPTION

The majority of marketed antibodies are labeled for intravenous (IV) administration; however, several antibodies have been approved for extravascular administration. For example, certolizumab pegol, adalimumab, efalizumab, and omalizumab are all approved for subcutaneous (SC) administration. Palivizumab is approved for intramuscular (IM) administration, and ranibizumab is administered by intravitreal injection. Antibodies have not been successfully developed for oral administration, as oral absorption of antibody is limited by presystemic degradation in the gastrointestinal tract and by inefficient diffusion or convection through the gastrointestinal epithelium. With the exception of ranibizumab, where intravitreal administration is employed to promote a regional effect, efficacy of mAbs following extravascular administration is dependent on systemic absorption.

Primary pathways for systemic absorption include convective transport of antibody through lymphatic vessels and into the blood, and diffusion of antibody across blood vessels distributed near the site of injection. Based on work conducted by Supersaxo et al.[5] that investigated the lymphatic uptake of a variety of proteins following SC injection in sheep, it has been suggested that the majority of antibody administered via SC or IM injection is absorbed via convection through lymphatic vessels. However, recent investigations conducted in rats suggest that the role of diffusion into blood vessels may be underestimated by the sheep studies.[6] Using insulin, bovine serum albumin, and erythropoietin as model proteins, Kagan et al. found that <3% of the administered dose of each protein was absorbed via the lymph. Neither Kagan et al. nor Supersaxo et al. have thoroughly investigated the fate of IgG following SC injection and, consequently, there is substantial uncertainty regarding the primary determinants of antibody absorption. The kinetics of antibody absorption, however, has been well described. After IM or SC injection, absorption proceeds slowly, and the time to reach maximal plasma concentrations (t_{max}) typically ranges from 2 to 8 days. Absolute bioavailability is generally reported between 50 and 100%.[3]

In practical terms, bioavailability is determined by the relative rates of presystemic catabolism and systemic absorption. Presystemic catabolism may be dependent on rates of extracellular degradation (e.g., via proteolysis), rates of antibody endocytosis (e.g., receptor-mediated, fluid phase), and rates of recycling through interaction with the Brambell receptor (FcRn). FcRn protects IgG from intracellular catabolism, and FcRn has been shown to be capable of transporting IgG across cell monolayers in both the apical-to-basolateral and basolateral-to-apical directions. Work from the Balthasar Laboratory (A. Garg, P.J. Lowe, and J.P. Balthasar, unpublished data) has indicated that the systemic bioavailability of 7E3, a monoclonal IgG1 antibody, was threefold higher in wild-type mice vs. FcRn-deficient mice (82.5 ± 15.6% vs. 28.3 ± 6.9%, $P < 0.0001$). It is not yet known whether the effects of FcRn on SC bioavailability are primarily related to FcRn-mediated protection from catabolism or from FcRn-mediated transport across the vascular endothelium (from interstitial fluid to the blood); however, the former mechanism is considered to be more plausible.

In some cases, an inverse relationship between SC bioavailability and antibody dose has been noted.[7] Such relationships are suggestive of saturable endocytosis and/or saturable degradation processes. Degradation at the injection site is likely to account for some presystemic loss of antibody, but the quantitative significance is uncertain. Charman et al. have demonstrated that the major determinant of the SC bioavailability of human growth hormone in sheep is presystemic catabolism during the course of lymphatic transport.[8] The role of lymphatic catabolism on the bioavailability of other proteins, including mAbs, is not known.

As a result of limited solubility of antibodies in solution (~100 mg/ml) and limitations on the volume of fluid that may be tolerated with IM or SC injection (~5 and 2.5 ml, respectively), IM and SC administration are feasible only for antibodies that demonstrate relatively high dose potency. Use of multiple injections may help to overcome this limitation, at least to some extent. For example, doses of 375 mg of omalizumab are routinely administered clinically, via three separate 1-ml SC injections.

Although they have not yet been employed in routine clinical use, there is substantial interest in the development of antibodies and Fc-fusion proteins for pulmonary delivery.[9] The lungs have a very large surface area and high perfusion rate. In addition, pulmonary epithelial cells are known to express FcRn, which may facilitate efficient systemic absorption of antibody delivered to the lung. As discussed with SC and IM administration, the feasibility of pulmonary delivery of antibodies is likely limited to those antibodies associated with very high dose potency, as only small volumes of fluid may be delivered to the lung.

ANTIBODY DISTRIBUTION

The distribution of mAbs is determined by the rate of extravasation in tissue, the rate of distribution within tissue, the rate and extent of antibody binding in tissue, and the rates of elimination from tissue. For large, polar substances such as mAbs, diffusion across vascular endothelial cells is very slow, and convection is believed to be the primary mechanism responsible for the transport of antibody from blood fluid to interstitial fluids of tissue. Of note, physiologically based analyses of antibody disposition in mice suggest that >98% of antibody enters tissue via convection.[10] The rate of extravasation by convective transport, or the movement of antibody into tissue by "solvent drag," is determined by the rates of fluid movement from blood to tissue and by the sieving effect of paracellular pores in the vascular endothelium. Sieving is thought to be largely determined by the size and tortuosity of the pores and by the size, shape, and charge of the solute (i.e., the antibody). Most physiologically based models of antibody disposition describe the uptake clearance for antibody extravasation as a product of the lymph flow rate (L) and an efficiency term ($1 − \sigma$). The reflection coefficient, σ, represents the fraction of solute sieved during the movement of solvent through a pore. In the case of mAbs, tissue reflection coefficients are often assumed to be equal in all tissues, with values in the range of 0.95–0.98.[10–12] However, it is likely that reflection coefficients may be much lower in tissues such as the

substances with several repeated epitopes, may bind with two or more antibodies, leading to the formation of large complexes that may be rapidly eliminated by phagocytosis. Elimination of large immune complexes may explain, in part, the nonlinear elimination kinetics of omalizumab and denosumab, which are thought to interact with soluble targets (IgE and receptor activator of nuclear factor-κB ligand). The majority of marketed antibodies demonstrate dose-dependent elimination consistent with target-mediated elimination, where clearance decreases as a function of dose (e.g., trastuzumab, rituximab, gemtuzumab, and panitumumab). Examples of state-of-the-art mathematical modeling of target-mediated antibody elimination include reports by Ng *et al.*, describing the nonlinear disposition of TRX1, an anti-CD4 mAb;[16] by Hayashi *et al.*, describing the nonlinear disposition of omalizumab, an anti-IgE mAb;[17] and by Lammerts van Bueren *et al.*, presenting an interesting conceptual model of target-mediated antibody elimination from a peripheral distribution compartment.[18]

IgG antibodies may also interact with Fc-γ-receptors (FcγR), and IgG-FcγR complexes may trigger endocytosis and catabolism. Considering the relatively high affinity of IgG for FcγR and the high endogenous concentrations of IgG in plasma (~65 μmol/l), it has been argued that FcγR-mediated elimination is unlikely to be important for monomeric IgG.[3] It is possible that FcγR-mediated elimination is significant, and perhaps dominant, in cases where antibody is able to form soluble immune complexes containing three or more IgG molecules, as well as in cases where antibody binds to cells suspended in blood or other body fluids (perhaps including viruses, bacteria, platelets, erythrocytes, and leukocytes). IgG "opsonized" particles are rapidly engulfed following engagement of FcγR on macrophages and on other phagocytic cells. This mechanism of elimination is well supported by the immunology literature; however, little work has been performed to link FcγR-mediated phagocytosis to the systemic pharmacokinetics of therapeutic antibodies. Additional study is required to allow meaningful discussion of the role of FcγR-mediated endocytosis in the elimination of such antibodies.

IgG, like other proteins found in plasma and interstitial fluid, may enter cells in all tissues via fluid-phase endocytosis. Interestingly, however, IgG differs from most proteins in that a significant fraction of endocytosed IgG is not sorted to the lysosome but is redirected to the cell surface and released into plasma or interstitial fluids. The recycling of IgG is mediated by the Brambell receptor, FcRn, which binds to IgG with pH-dependent affinity.[19,20] Within the acidified environment of the early endosome, IgG binds tightly to FcRn. The IgG–FcRn complexes are not delivered to the lysosome for catabolism but rather are sorted to the cell surface for fusion with the cell membrane. The receptor shows virtually no affinity for IgG at physiological pH and, upon fusion of the sorting vesicle with the cell membrane, IgG dissociates from the receptor and is rapidly released into extracellular fluid.

FcRn-mediated recycling of IgG appears to be quite efficient based on studies conducted with knockout mice. In animals lacking expression of FcRn, IgG clearance is increased

by approximately tenfold,[20] which would be consistent with a recycling efficiency of 90% (i.e., in wild-type animals expressing FcRn). Because FcRn expression is limited, FcRn-mediated recycling is capacity limited. The average concentration of IgG in plasma in humans is ~10 mg/ml. At this concentration, IgG has a half-life of ~25 days[21] and a plasma clearance of ~10 ml/h (~3.5 ml/kg/day). High concentrations of IgG are able to saturate the recycling system, decreasing recycling efficiency and leading to an increase in the fractional catabolic rate of IgG. For example, in myeloma patients, where IgG concentrations in plasma may approach 100 mg/ml, IgG half-life decreases to 8–10 days. Conversely, in patients with very low plasma concentrations of IgG, the half-life of IgG antibody may be >70 days.[21]

IgG affinity for FcRn is species specific. Human FcRn shows high affinity for human IgG and also for IgG from guinea pigs and rabbits; however, the human receptor shows very little affinity for IgG derived from most other species, including mice and rats.[22] The low affinity of human FcRn for mouse IgG helps to explain the very rapid elimination of murine mAbs in humans. Approved murine monoclonal IgGs (e.g., muromononab-CD3, ibritumomab) demonstrate half-lives of ~1 day in patients, whereas human IgG is typically associated with a half-life of ~25 days.

Although FcRn recycling is capacity limited, significant alteration in the efficiency of FcRn recycling is not typically achieved with therapeutic doses of mAbs. Most mAbs are administered at doses of <10 mg/kg, which will increase the total IgG "body load" by <1–2%, as humans typically possess 50–100 g of endogenous IgG. However, high-dose intravenous immunoglobulin (IVIG) therapy, which calls for the administration of 2 g/kg of pooled human IgG, increases IgG plasma concentrations sufficiently to increase IgG clearance approximately threefold.[23] This increase in IgG clearance leads to a decrease in endogenous antibody concentrations; consequently, IVIG therapy for the treatment of autoimmune conditions may achieve effects by decreasing the plasma concentrations of endogenous, pathogenic autoantibodies. Although IVIG therapy is an effective treatment of a variety of autoimmune conditions, it is very expensive because of the high doses of antibody required. Of note, preclinical experiments have demonstrated that anti-FcRn antibodies are able to achieve effects similar to those of IVIG therapy, at dose levels that are ~100-fold lower than those required for use in IVIG therapy.[24] There is significant interest in the development of specific FcRn inhibitors for use in the treatment of autoimmunity.[25]

IMMUNOGENICITY

Any exogenous protein may be viewed by the body as foreign and trigger immune responses that lead to the generation of endogenous antibodies against the protein. Therapeutic antibodies are no exception. mAb drugs may be categorized as (i) rodent antibodies, which are typically obtained from murine or rat hydridomas; (ii) chimeric antibodies, which are derived from chimeras that have been engineered to express IgG antibodies with human constant regions and rodent variable regions; (iii) CDR-grafted antibodies, which contain specific regions within rodent variable domains, the CDRs, grafted onto a human IgG

such as volume of each compartment (organ) and blood flow rate, are used to build the model and predict human pharmacokinetics. A significant advantage of the PBPK approach is that it allows prediction of antibody levels in many tissues, including tumor. PBPK models are ideally suited to the consideration of effects of saturable processes (e.g., target binding, FcRn processing) on antibody pharmacokinetics, and these models are also well suited to predict the influence of a variety of factors (e.g., antigen expression, antibody affinity) on the tissue selectivity of antibody disposition. Recent PBPK models have incorporated FcRn-antibody binding, allowing consideration of the effects of FcRn on antibody catabolism and distribution.[11,12] The limitations for use of PBPK models to predict the disposition of antibodies in humans are significant, however. PBPK models are complex, mathematically difficult to construct, poorly suited to population analyses, and often limited because of a lack of tissue concentration data, parameter availability, or parameter identifiability.

Despite the large number of antibodies in development, only a handful of reports using preclinical data to predict the clinical pharmacokinetics of antibodies have been published, perhaps indicating the difficulties associated with the interspecies scaling of antibody disposition. Any effort to predict human pharmacokinetics based on preclinical disposition data should consider possible species differences in the expression or turnover of the target receptor, antibody affinity for the target, antibody-FcRn binding, endogenous IgG concentrations (i.e., as a determinant of FcRn saturation), and potential effects of host anti-drug antibodies.

PHARMACODYNAMICS

mAbs have been marketed for use in the treatment of a wide range of conditions, including cancer, autoimmunity, and inflammatory diseases. It is convenient to discuss antibody pharmacodynamics relating to four main categories of applications: (i) immunotoxicotherapy, where antibody is employed to alter the pharmacokinetics and pharmacodynamics of soluble ligands (e.g., drugs, xenobiotics, and cytokines); (ii) elimination of target cells; (iii) alteration of cellular function (e.g., receptor blockade); and (iv) targeted drug delivery.[3]

Antibodies used for immunotoxicotherapy include bevacizumab, adalimumab, ranibizumab, omalizumab, and infliximab. Each of these antibodies binds to a soluble ligand (e.g., vascular endothelial growth factor or tumor necrosis factor) and alters the pharmacokinetics and pharmacodynamics of the ligand. These "neutralizing" antibodies act as competitive inhibitors of ligand-receptor binding, shifting ligand concentration–effect relationships. In addition, by binding to soluble ligand, immunotoxicotherapies often produce dramatic alterations in ligand pharmacokinetics. In most cases, the anti-ligand antibody will decrease the unbound fraction of ligand in plasma, decrease the ligand volume of distribution and clearance, and increase the half-life of the ligand. For example, omalizumab, an anti-IgE mAb, dramatically decreases the clearance of its target ligand, leading to a fivefold increase in the plasma half-life of IgE.

PK/PD models for omalizumab and infliximab have been published recently.[38,39] In each model, a second-order association

function was employed to describe the formation of antibody–ligand complexes, and complexes dissociated via a first-order process. The models are nonlinear with respect to antibody-ligand binding because of the second-order nature of the binding process, as well as capacity limitations associated with the available concentrations of ligand and antibody. The models relate unbound ligand concentration to the effect of interest; as such, the models link the PK effects of the anti-ligand antibody to the pharmacodynamics of the ligand. Of note, the models differ substantially in terms of their characterization of the fate of the antibody–ligand complex. In the infliximab model, it was assumed that the antibody–ligand complex was eliminated with the same fractional catabolic rate as the unbound ligand, tumor necrosis factor-α. Fitting the model parameters to the data resulted in an estimation of a 30–40-day half-life for tumor necrosis factor-α, which is considerably different from the known value (<1 h). The omalizumab model, which is much more plausible, does not assume an equivalent elimination rate constant for the complex and the ligand (IgE) but allows for kinetically distinct elimination of IgE, omalizumab, and the IgE–omalizumab complex.

The recent work of Marathe et al., which describes the PK/PD of denosumab, a monoclonal IgG2 antibody directed against the receptor activator of nuclear factor-κB ligand, represents the state of the art in modeling immunotoxicotherapies (**Figure 2**).[40] The receptor activator of nuclear factor-κB ligand is thought to be a soluble ligand, but there is some possibility that the protein is also expressed on the cell surfaces. Denosumab pharmacokinetics were captured with a target-mediated disposition model, and denosumab pharmacodynamics were described with a model that relates the unbound concentrations of denosumab to the inhibitory effect of the antibody on the receptor activator of nuclear factor-κB ligand binding. This mechanistic model provided an excellent description of the pharmacokinetics and pharmacodynamics of denosumab in multiple myeloma patients.

Several antibodies, including rituximab, cetuximab, and trastuzumab, are designed to bind to cell-surface proteins to mediate
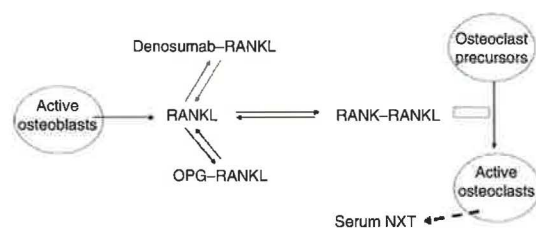

Figure 2 Pharmacodynamic model for denosumab. Marathe et al. provide an excellent example of a pharmacodynamic model for an antibody acting as an antagonist of a soluble ligand.[40] Denosumab, like other antibodies used for immunotoxicotherapy, binds to a soluble ligand (receptor activator of nuclear factor-κB ligand, RANKL), preventing the ligand from binding to its endogenous receptor (receptor activator of nuclear factor-κB, RANK), and antagonizing the effect of the ligand (i.e., inhibiting RANKL stimulation of osteoclast maturation). The Marathe et al. model, which has been simplified herein, employs equilibrium binding functions to relate plasma concentrations of denosumab, RANK, and the natural RANKL antagonist (osteoprotegrin, OPG) to unbound concentrations of RANKL, and to the measured biomarker (serum N-telopeptide, NTX).
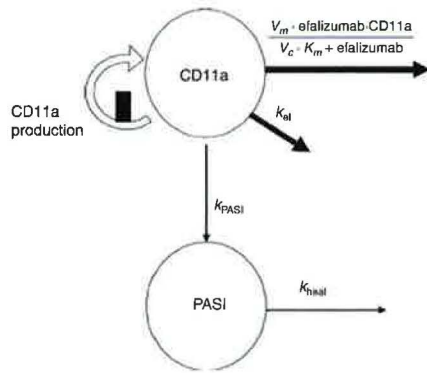
Figure 4 Pharmacodynamic model for efalizumab. The Ng *et al.* model, selected as an example model for antibodies that alter cellular function, describes the effects of efalizumab on CD11a expression, elimination, and the psoriasis area and severity index (PASI). The model allowed excellent characterization of efalizumab pharmacodynamics in a large, population pharmacokinetic and pharmacodynamic analysis. The figure shown is a simplified version of the model presented by Ng *et al.*[48]

the psoriasis area and severity index, an efficacy end point for psoriasis (**Figure 4**).[48]

Preclinical modeling examples include a report by Luo *et al.* that describes the development of a model of cetuximab PK/PD using data collected from studies conducted with a murine colon carcinoma xenograft model.[49] Although the antibody demonstrates nonlinear, target-mediated disposition in humans, cetuximab pharmacokinetics were dose-proportional in the mouse model and were well characterized with a linear, one-compartment model. Cetuximab's effects on the phosphorylation of the epidermal growth factor receptor were captured with an indirect effect model, which allowed comparison between estimated values of EC_{50} and EC_{90} (half maximal effective concentration and 90% effective concentration, respectively), plasma concentrations of cetuximab achieved in patients, and the efficacy of cetuximab in clinical trials.

In comparison with the other main categories of antibody usage, relatively little success has come from the development of antibodies for targeted drug delivery. Most of the interest in this area has centered on the development of conjugates of antibodies and toxic agents (e.g., chemotherapeutic drugs, radioisotopes, and biological toxins), with the intent of using the high specificity and selectivity of antibodies to mediate targeted delivery of toxins. The antibody–toxin conjugates, or immunotoxins, carry the complexities shared by other types of antibody drugs (e.g., potential for nonlinear target-mediated disposition, immunogenicity). In addition, off-target toxicity is often a greater concern for immunotoxins because of the potential for dissociation, *in vivo*, of the toxin from the antibody and because of the high potency of toxins employed. Considerable toxicity often results from "nonspecific" distribution of the immunotoxin to off-target sites. Bone marrow stem cells are particularly susceptible to toxicity from immunotoxins because of their rapid growth rate and high sensitivity to chemotherapy, along with the leaky vasculature of the bone marrow, which allows relatively efficient convective uptake of immunotoxins.

Most of the work associated with the use of antibodies for targeted drug delivery has been focused on the treatment of solid tumors. Solid tumors are problematic targets for antibody drugs, as tumor growth often leads to the collapse of lymphatic vessels within the tumor, which leads to an increase in the tumor interstitial pressure. High interstitial pressure minimizes the blood-to-tumor hydrostatic pressure gradient, and this decreases the driving force for antibody uptake into tumor by convection. Once antibody extravasates, distribution may be limited by the binding-site barrier (discussed above), further reducing the effectiveness of antibody-directed delivery of toxins to solid tumors.

For chronic immunotoxin therapy, it may be important to select a cellular target that is easily accessed by antibody in blood (i.e., hematological cells, cells in tissues with "leaky" vasculature), antibodies with little risk for immunogenicity, toxins with little risk for immunogenicity (e.g., protein toxins such as ricin would not be desired), and conjugation chemistry that allows for little off-target release of toxin, but where there is efficient release of toxin within target cells (i.e., in cases where this is required for efficacy). Successfully marketed antibodies include gemtuzumab ozogamicin, tositumomab, and ibritumomab tiuxetan. In each case, the antibodies target hematological cells. Tositumomab and ibritumomab utilize radioisotope toxins, where dissociation from the antibody is not required for the desired cytotoxic effect. Gemtuzumab ozogamicin employs a calicheamicin derivative toxin that is released in target cells after binding of gemtuzumab to the target receptor (CD33) and after receptor-mediated endocytosis of the immunotoxin. The toxin migrates to the nucleus and binds DNA, leading to double-strand breaks and cell death.

There are few publications of PK/PD models for immunotoxin therapies. Ideally, mathematical models of immunotoxin pharmacokinetics and pharmacodynamics should account for the intact immunotoxin, "naked" antibody (i.e., antibody alone, following release of the toxin), and "free" toxin. In an interesting example, Zhu *et al.* applied physiologically based modeling and simulation to investigate relationships between the dose of radioimmunotoxins and uptake of the conjugates into tissue.[50] Their modeling led to the conclusion that Fab fragments would be preferred for use in detection of tumors, whereas Fab2 fragments were predicted to be more effective for use in radioimmunotherapy.[50] The structure of their PBPK model may be easily adapted to the prediction and characterization of the PK/PD of additional immunotoxins.

CONCLUSIONS

Antibody drugs demonstrate unique, complex PK characteristics. Absorption following IM or SC administration is slow and, for some antibodies, dose dependent. Antibody distribution kinetics is influenced by rates of convective transport, binding to tissue sites, and rates of catabolism within tissue. Traditional noncompartmental analyses and mammillary models may underestimate the steady-state distribution volume of many antibodies, particularly those associated with substantial elimination from tissue sites. Antibodies often demonstrate target-mediated disposition,

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