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Elimination mechanisms of therapeutic monoclonal antibodies

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Targeted therapies using monoclonal antibodies have achieved important therapeutic applications in the treatment of various human diseases. Understanding the factors that impact the pharmacokinetics of monoclonal antibodies is of high importance for effective therapy. Many factors related to the target antigen, antibody and patients can affect antibody elimination. Evaluation of these factors will facilitate the understanding of the processes involved in antibody elimination.

Targeted therapies using monoclonal antibodies (mAbs) have gained increased therapeutic application in recent years. Seventeen[1] mAbs are currently approved in the USA in various therapeutic areas, such as oncology, inflammation, infectious disease and cardiovascular disease. All approved mAbs are of the IgG class. Thirteen are intact mAbs, three are conjugated and one is a mAb fragment (Fab). In the next five years the number of approved mAbs might potentially double [1]. The clinical pharmacology of therapeutic mAbs has been reviewed in a recent article [2]. A feature of mAb therapeutics is the high specificity conferred by the antibody interaction (variable region paratope) with a specific region on the targeted antigen (epitope). Hence, it is not surprising that among the factors regulating mAb pharmacokinetics, antigen properties, such as antigen distribution (soluble versus membrane associated) and antigen concentration, can influence mAb pharmacokinetics. Other factors, such as mAb structure and engineering, host factors, concurrent medications and immunogenicity, can alter the pharmacokinetic profile [2–4]. Understanding the factors that affect the pharmacokinetics of mAb is of high importance for effective therapeutic application.

Antibody structure and function

Antibodies serve two important functions: they bind and modulate antigens and they bind complement and immune effector cells, such as natural killer cells and monocytes. Each IgG molecule contains two identical heavy chains and two identical light chains (Figure 1). Antibody structure has evolved to accommodate the diverse antigen binding specificities through the 'variable region'. The antigen binding site is formed by the intertwining of the light chain variable domain (V_L) and the heavy chain variable domain (V_H). Each V domain contains three short stretches of peptide known as the complementarity determining regions (CDRs); the CDRs are the prominent determinants of antigen binding affinity and specificity. The light chain contains one constant domain: C_L. The heavy chain contains three constant domains: C_H1, C_H2, and C_H3. The C_H2 and C_H3 domains allow interactions of the IgG molecule with various components of the immune system by either binding C1q, which activates the complement cascade and elicits complement-dependent cytotoxicity, or by binding to Fcγ receptors on immune effector cells, which elicits antibody-dependent cellular cytotoxicity. These same variable and constant domains of the molecule also affect IgG catabolism and elimination [2,4,5].

Major determinants of monoclonal antibody elimination

Constant region: interaction with Fc receptors

Salvage pathway

IgG is the most abundant serum immunoglobulin (average concentrations ~11–14 mg/ml [6]) and serum IgG homeostasis is of

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[1]The total number of approved therapeutic monoclonal antibodies in the USA reached eighteen in 2005; however, one antibody was withdrawn from the market in the same year.

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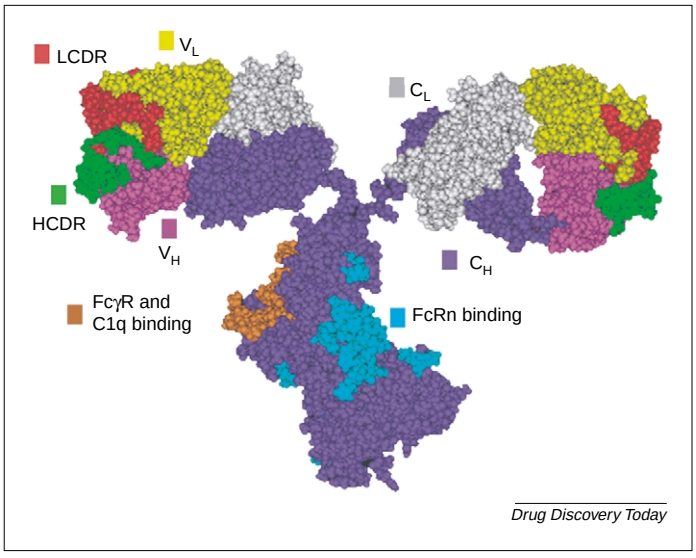

FIGURE 1

Representation of the space-filling model of an IgG molecule. Abbreviations: LCDR and HCDR, complementarity determining regions on V_L and V_H domain.

particular importance in mediating humoral immunity. The protective role of neonatal Fc receptor (FcRn), a major histocompatibility complex class-1-related receptor, in regulation of IgG homeostasis was postulated by Brambell [7]. Recent studies have further clarified the details of Brambell hypothesis and indicated that FcRn functions as a salvage receptor which regulates IgG catabolism [8–10]. Mice genetically lacking expression of FcRn demonstrated IgG hypercatabolism and faster IgG elimination [11].

Engineered human IgG antibodies with altered affinity to human FcRns [12–15] have altered elimination rates. Binding of IgG to FcRn is pH dependent: IgG binds to the receptor under mildly acidic conditions and is released under slightly basic conditions [14]. Mutation of IgG Fc residues (amino acid positions 428 and 250, alone or in combination) that increased the binding affinity of the antibody for FcRn (4- to 27-fold better binding affinity to rhesus FcRn than the wild-type antibody at pH = 6.0) without impacting the pH-dependent binding properties resulted in a twofold increase in serum half-lives of the mutant IgG2 antibodies [13]. The rapid clearance of murine IgGs from human circulation [16,17] has been attributed to the selectivity of human FcRn binding to human IgG. Administration of a murine anti-FcRn antibody against rat β_2-microglobulin transiently increased the clearance of a murine IgG antibody [18], which also supports the significance of FcRn in regulating antibody catabolism. In addition, antibody fragments, such as Fab (monovalent antibody fragment), $F(ab')_2$ (divalent antibody fragment) and scFv (single chain variable fragment) that lack the Fc domain and do not bind to FcRn, have substantially shorter half-lives (0.5–30 h) than the intact IgG. The low molecular weight antibody fragments are also subject to renal clearance [2].

Further evidence for the regulatory role of FcRn on IgG clearance is provided by studies involving patients with autoimmune disorders, who have received intravascular immunoglobulin treatment [19]. High levels of IgG saturate FcRn and block the salvage pathway. Earlier investigations demonstrated that the clearance rate of IgG was greatly dependent on its serum concentration, whereas the concentration impact on clearance did not apply to other immunoglobulin subclasses, such as IgM and IgA [20]. Longer IgG half-lives were reported at lower IgG concentrations, consistent with Brambell hypothesis for the protective role of FcRn on IgG homeostasis [7,20]. The impact of serum IgG concentrations on IgG clearance was recently demonstrated in experimental models. Administration of a large dose of purified human IgG (~2 g/kg) in mice resulted in a rapid decrease (>60%) in baseline mouse IgG1 and IgG3 serum concentrations [21]. Recently, similar results were reported for the effect of large dose of human IgG (2 g/kg) on the clearance of an anti-platelet antibody in rats [22].

Normal variation in endogenous IgG levels might not affect the elimination rate of therapeutic antibodies; likewise, the usual therapeutic doses of mAbs [2] are not expected to increase total IgG levels to the point that IgG clearance is affected. Recently, we had the opportunity to examine the impact of baseline serum IgG concentrations on clearance of a fully human IgG2 antibody against human interleukin (IL)-8 generated using Xenomouse® technology [23,24]. Following administration of multiple doses of the antibody (200 to 400 mg/patient, administered monthly or every three weeks, for three or four doses) in patients with inflammatory diseases, such as psoriasis, rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD), steady-state serum antibody concentrations (200–50 μg/ml) were achieved [25]. Baseline serum IgG concentrations ranged between 10 mg/ml and 50 mg/ml in patients with psoriasis and RA (Figure 2). However, no correlation between serum IgG and the steady-state antibody clearance was observed. Population pharmacokinetic analysis further verified the lack of correlation between serum IgG and steady-state antibody clearance.

Impact of effector function on pharmacokinetics and pharmacodynamics

In addition to FcRn, three classes of Fc receptors (FcγRs) for IgG interactions have been identified in humans. These receptors are expressed by various phagocytic cells, such as monocytes, macrophages, neutrophils and eosinophils, and other cells of the immune system, such as B and T cells, as well as platelets [26]. However, expression profiles and variability in distribution of the three FcγRs on various cell types are heterogeneous and complex and further compounded by genetic polymorphism (characterized by multiple sub-isoforms) observed among different individuals [27,28]. Human FcγRs bind IgG with various degrees of affinity, ranging from low ($>10^{-7}$ M) for FcγRII (CD32), medium ($=10^{-7}$ M) for FcγRIII (CD16), to high (10^{-8}–10^{-9} M) for FcγRI (CD64) [28,29].

Different IgG isotypes, such as IgG1, 2, 3, and 4, demonstrate unique recognition and activation profiles when interacting with various FcγRs [2,28–30]. Because of different interaction profiles with FcγRs, IgG1 subclass has proved to be most effective in complement dependent (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). This, indeed, is inline with the function of this highest-circulating serum IgG subclass (IgG1; 60–70% of total serum IgG [6,29]) for binding exogenous pathogens and for effective destruction and clearance of antigens via activation of various effector mechanisms [28,29]. With respect to effector functions, IgG3 has been shown to be as effective as IgG1 in complement activation and cell-mediated toxicity, whereas IgG2 and IgG4 isotypes are relatively inactive in eliciting effector functions [28–30]. In addition to their contributions to mAb pharmacological activities (pharmacodynamics), the FcγRs could also regulate elimination and pharmacokinetics (PK) of mAbs.

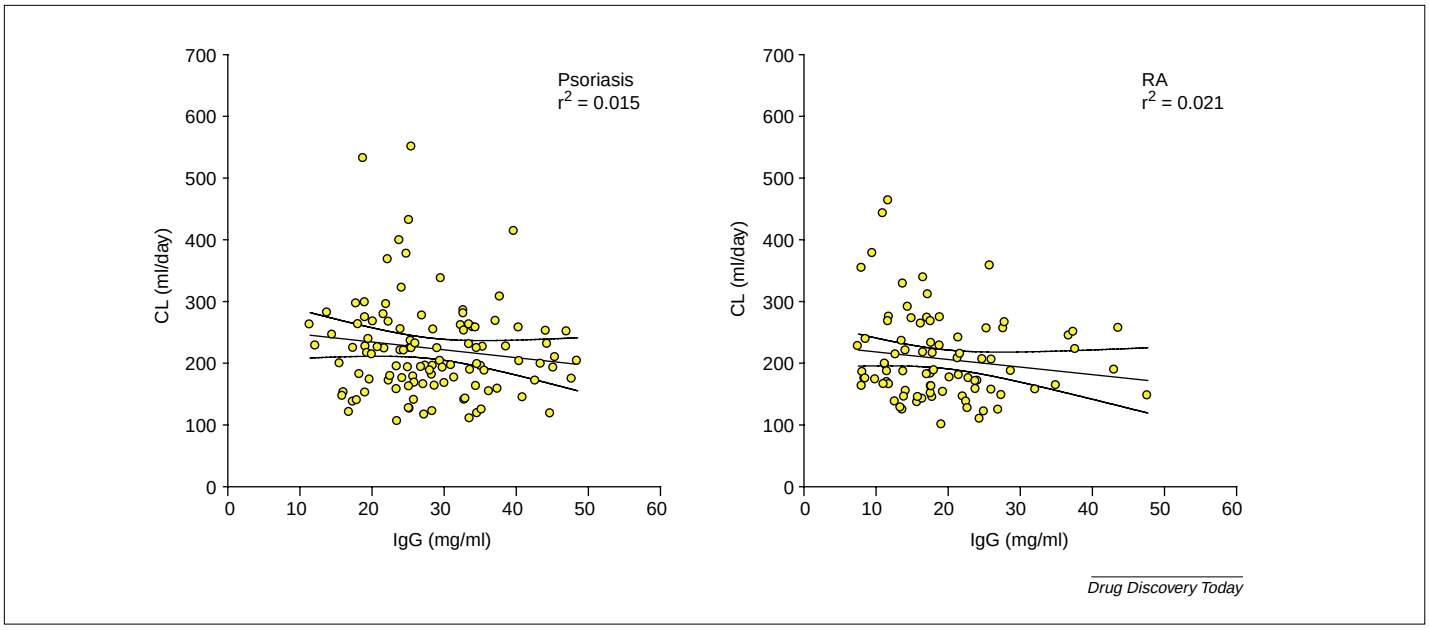

FIGURE 2

Relationship between baseline serum IgG concentrations and steady-state anti-IL8 antibody (ABX-IL8) clearance in patients with psoriasis and RA. Baseline serum IgG concentrations ranged between 10 mg/ml to 50 mg/ml in patients with psoriasis and RA. Following administration of multiple doses of the antibody (200–400 mg/patient, administered monthly or every-three-weeks, for three to four doses) in patients with psoriasis and RA, steady-state serum antibody concentrations (200–50 μg/ml) were achieved and antibody clearance (CL) was estimated from the steady-state serum antibody concentrations.

Pharmacodynamics

Antibodies can exert their pharmacological effects via several different mechanisms: (i) neutralizing antigen function, (ii) activating receptors by mimicking endogenous receptor ligands, (iii) delivering toxins to specific cells (targeted delivery) and (iv) eliciting effector functions in conjunction with antigen modulation [2,31]. Under some circumstances, where antigen expression is high in crucial organs (e.g. heart, lung and vasculature), effector function might not be desirable and could be deleterious; however, in other instances (such as applications in hematological malignancies) effector functions might be a significant part of the mechanism of action and maximizing the antibody effector functions might be highly desirable.

The binding sites on human IgG1 for human FcγRs have been mapped and alterations of crucial residues in Fc region (CH_2 domain or the hinge region joining CH_1 and CH_2) have enhanced or decreased ADCC and CDC activity [15,32–34]. Alterations of residues located at the CH_2 domain of IgG1 involved in binding with C1q protein, a component of the complement activation cascade, resulted in a significant increase in CDC activity [15]. The functions associated with IgG1 binding to Fcγ receptor have been delineated for the anti-CD20 antibody, rituximab, in preclinical and clinical studies. FcγRIIb is the inhibitory receptor that modulates activity of FcγRIII. In FcγRIIb-deficient mice improved antitumor activity was observed following administration of the anti-CD20 antibody [35]. Clinically, polymorphism in FcγRIIIa is associated with a better therapeutic response following rituximab administration in non-Hodgkin's lymphoma patients [36]. The more-favorable outcome in patients with FcγRIIIa receptor 158v allotype was partially attributed to a higher affinity of the variant receptor for binding to human IgG1 isotype and to an increase in antibody-dependent cellular cytotoxicity [36,37].

Pharmacokinetics

Clearance of antibodies through the cells of the reticuloendothelial system (RES) can be regulated through the interaction with various Fc receptors. FcRns are expressed on phagocytic cells of the RES and protect IgG from rapid clearance. Similarly, cells of the RES express various types of Fcγ receptors. Interactions of IgG antibodies with this subset of receptors could potentially impact antibody clearance. As discussed, polymorphism in Fcγ receptors impacted the therapeutic response to rituximab [36,38]. Although the favorable clinical outcome was attributed to a more-efficient FcγRIIIa-dependent cytotoxicity, it is not clear if polymorphism in Fcγ receptors could have any potential impact on antibody clearance. Polymorphism in FcγRIIIa was shown to impact *in vivo* clearance of red blood cells (RBC) coated with an anti-D IgG3 antibody in humans [39]. The faster clearance was attributed to a more-efficient elimination of opsonized RBC by phagocytic cells in spleen of the subjects homozygous for FcγRIIIa-F/F158 [39]. These results are consistent with previous data demonstrating the impaired clearance of IgG-sensitized RBC in the presence of an anti-FcγRIIIa antibody [40]. In addition, downregulation of Fcγ receptor on cells of monocyte lineage by immunomodulatory drugs, such as methotrexate (MTX), might potentially impact the clearance of mAbs such as adalimumab (see Section 'concomitant medications').

Host factors and IgG isotype

Antibody clearance could be impacted by factors that are related to the antibody isotypes as well as host-related factors. Among IgG antibodies, human IgG1, 2, and 4 exhibit long elimination half-lives of ~3 weeks in humans, which has been attributed to interactions with FcRn. The half-life for human IgG3 is reported to be approximately one week in humans. The shorter half-life of this IgG isotype has been attributed to the binding differences to FcRn, as a

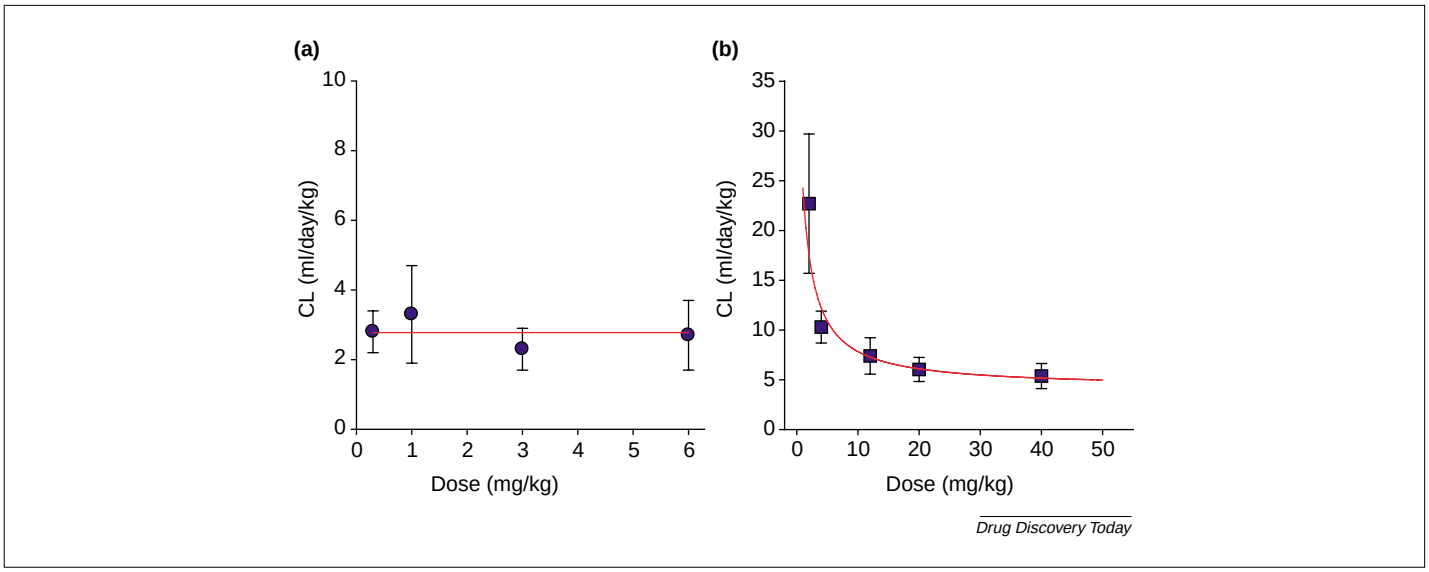

FIGURE 3

Relationship between mAb clearance and antibody dose following administration of mAb single intravenous doses. (a) The relationship between clearance (CL) and dose for the fully human antibody, ABX-IL8, against a soluble, circulating antigen IL8 following administration of single doses. The clearance value across the administered doses represents the nonspecific (non-antigen-mediated) clearance by the RES in humans. **(b)** The relationship between clearance and dose for the fully human anti-CD146 antibody against a membrane-associated, internalizing antigen CD146 following single dose administration. The high antibody clearance at low doses represents the impact of the antigen on antibody clearance. At higher doses, when the antigen sink is saturated, the clearance value approaches the nonspecific clearance by the RES.

result of a single amino acid difference in the FcRn binding domain [9].

Host-related factors could also impact antibody clearance. A review of the marketed intact antibodies reflects that half-lives of murine antibodies are much shorter than those reported for chimeric or humanized antibodies in humans: murine (~2–3 days) < chimeric (~8–10 days) < humanized (~20–23 days). The rapid elimination of murine IgGs from human circulation has been attributed to lack of binding to human FcRn. Although murine FcRn binds human IgG, resulting in a long half-life of human IgG in mice, the lack of human FcRn binding to murine IgG was confirmed using a transgenic mouse model expressing human FcRn [17].

High concentrations of rheumatoid factors found in RA patients could potentially impact IgG clearance. Rheumatoid factors, which are usually low-affinity IgM anti-IgG Fc auto-antibodies, bind the Fc region in the CH_2–CH_3 domains and, hence, could impact IgG binding to Fc receptors. Based on our recent experience, no differences in the clearance of anti-IL-8 IgG2 (ABX-IL8) antibody was observed in patients with RA in the presence of rheumatoid factors versus that observed in psoriasis or COPD patients with no detectable serum rheumatoid factors. In addition, no apparent correlation between baseline serum rheumatoid factor concentration and steady-state antibody clearance in RA patients was observed (unpublished results). However, minor increases in the clearance of adalimumab, an IgG1 antibody, have been reported in RA patients with high rheumatoid factor levels (adalimumab prescribing information).

Variable region: interaction with antigens

Elimination of mAbs might be impacted by interactions with the target antigen. When the antigen alters the clearance of mAb, the effect is usually manifested as a dose-dependent clearance rate and half-life. At low mAb doses that do not saturate the antigen, the half-life is shorter than the one observed for endogenous IgG; as the mAb dose is increased and antigen is progressively saturated, an increase in half-life and decrease in clearance rate is observed. The antigen-dependent clearance pathway is often referred to as an 'antigen sink'. Antigen sinks are most commonly observed for mAbs targeting internalizing membrane antigens with high normal-tissue expression.

Soluble antigens

Antibodies raised against soluble antigens, such as circulating cytokines [e.g. vascular endothelial growth factor (VEGF), IL-8, IL-5 and IL-4], have undergone extensive research in animal and clinical studies [24,25,41–44]. Although different IgG isotypes (IgG1 and 2) have been used against various targets, similarities in the PK profiles are evident. Following single-dose administration of mAbs, dose-proportional, linear clearance has been observed [41–44]. In general, the PK profile is characterized by a two-compartment linear model with a rapid elimination phase, characterized by a short distribution phase, and more-prolonged elimination half-life, as a result of the nonspecific clearance by the RES and the interaction with FcRn. The distribution volume parallels the plasma and extracellular fluid volume, representing limited distribution of the antibody.

The relationship between clearance and dose for the fully human anti-IL8 mAb, ABX-IL8, [24,25] following administration of a single dose in psoriasis patients is shown in Figure 3a. The clearance and steady-state distribution volume in human were predicted with high accuracy from studies conducted in rats (a species that does not express an IL-8 orthologue) and cynomolgus monkeys (a species expressing an IL-8 homolog that cross-reacts with ABX-IL8), using the following allometric scaling equations:

$CL = 6.8 \times (\text{Body weight})^{0.86}$; $V_{ss} = 72 \times (\text{Body weight})^{1.01}$

indicating that the PK parameters such as clearance (CL) and steady-state volume of distribution (V_{ss}) across species could be scaled up or down by correcting for body weight differences. The clearance value across the administered doses represented the

nonspecific (non-antigen-mediated) clearance by the RES in humans. A similar property has been observed for other mAbs, such as a humanized mAb against VEGF, and for other proteins [43,45].

Immunoassay-based analytical methods for quantitation of therapeutic mAb levels in serum frequently use the antigen as a capture reagent. Because antigen bound to antibody will compete with mAb by binding to the capture reagent, this assay format will reflect unbound serum concentrations of mAb. In principle, nonlinearity in the pharmacokinetic profile can be observed but should not be mistaken for antigen-mediated elimination mechanisms.

Membrane associated antigens

In contrast to soluble antigens, membrane-associate internalizing antigens can greatly enhance the antibody clearance through a target-mediated, specific process. When antigen contributes to antibody clearance, total clearance is a result of a specific, saturable antigen-related pathway and a nonspecific linear clearance pathway mediated by the RES (Figure 4).

The antigen-mediated clearance pathway is mediated by the binding of the antibody to the antigen and subsequent internalization of the antibody–antigen complex, which is followed by degradation of the internalized antibody and antigen. The contribution of the antigen to mAb clearance depends on various antigen-related factors, such as antigen concentration and distribution, antigen internalization rate and antigen turnover rate. The impact of the antigen on mAb pharmacokinetics is generally characterized by a high mAb clearance at lower antibody doses. At higher antibody doses, a decrease in clearance is observed, with clearance approaching the nonspecific mAb clearance by the RES because of dose-dependent saturation of the antigen sink (Figure 3b).

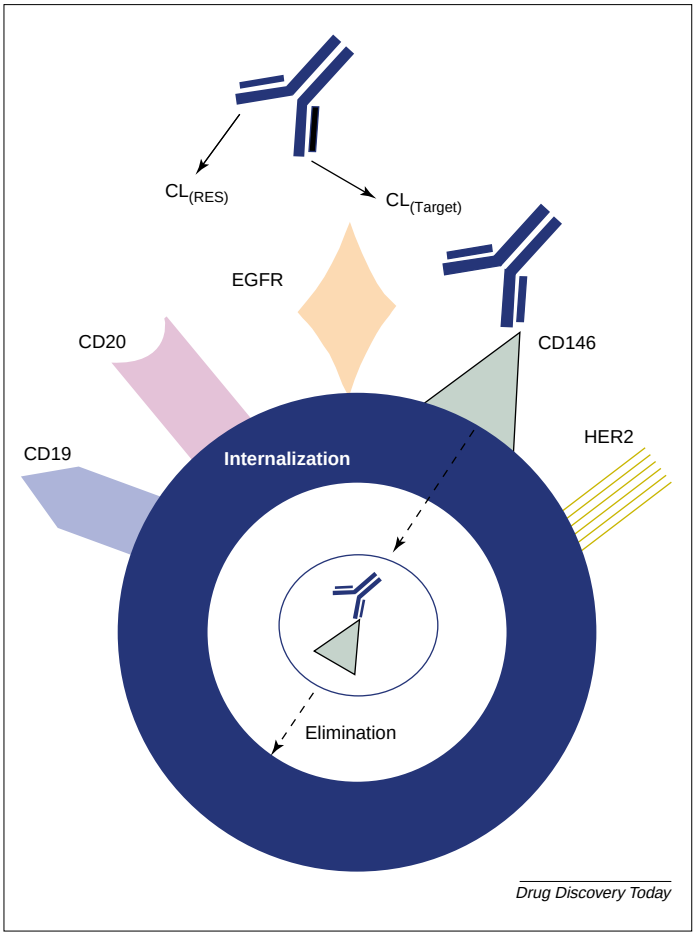

FIGURE 4

Target-mediated clearance of mAb. When target impacts mAb clearance, total clearance (CL_T) is a combination of two different clearance pathways: (i) the specific pathway, which is nonlinear and saturable and is attributed to the antigen, and (ii) the nonspecific pathway, which is linear and attributed to the RES: $CL_T = CL_{(RES)} + CL_{(Target)}$. CD19, CD20, EGFR, CD146 and HER2 are examples of cell membrane antigens that affect the clearance of mAbs directed against those targets.

The impact of antigen-mediated clearance on antibody pharmacokinetics has been observed with marketed antibodies against targets such as human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), CD20 and investigational mAbs against membrane-associated antigens such as CD146. HER2 is an internalizing transmembrane receptor that belongs to the epidermal growth factor receptor family and is expressed in human breast cancer [46]. Trastuzumab is a humanized mAb developed to target HER2 and is currently marketed in USA (trastuzumab prescribing information). A decrease in the clearance of trastuzumab has been reported with increases in antibody dose [46]. A similar non-linearity was reported in the clearance of cetuximab (chimeric IgG1) and panitumumab (fully human IgG2) antibodies that target EGFR. A 65–75% decrease in the clearance of panitumumab and cetuximab was reported with a 2.5- and 10-fold increase in weekly administered dose, respectively (cetuximab prescribing information; [47]).

Following administration of multiple doses of anti-CD20 antibody, rituximab, in lymphoma patients, a 2.5 times increase in the half-life parameter was observed following administration of the fourth weekly dose (rituximab prescribing information). The change in the half-life following administration of anti-CD20 antibody was partially attributed to reductions in tumor burden (CD20-positive cells) in patients following rituximab therapy (rituximab prescribing information). Similarly, following single-dose administration of a fully human anti-CD146 antibody, a dose-dependent decrease in mAb clearance was observed (Figure 3b).

The clearance of a fully human mAb against EGFR, panitumumab, was compared in nude mice and cynomolgus monkeys. Panitumumab crossreacts with monkey EGFR but does not cross-react with murine EGFR. The relationship between panitumumab clearance and dose following administration of single intravenous doses of panitumumab is shown in Figure 5. Non-linearity in the clearance of panitumumab was observed in monkeys, consistent with the presence of saturable EGFR sink. At high doses in monkeys, the clearance approached the rate associated with clearance by the RES. In mice, the clearance was linear and consistent with the activity of the nonspecific RES clearance pathway. These results support the contribution of antigen-mediated clearance in species expressing crossreactive EGFR.

Special patient populations

The effects of demographic variables, such as age, gender, renal and hepatic function, on the pharmacokinetics of mAbs are controversial. Available data highlight an inverse relationship between clearance of adalimumab and patient age (adalimumab prescribing information). However, for other mAbs such as trastuzumab or bevacizumab no correlation between mAb clearance and patient age, gender or serum creatinine was reported (bevacizumab and trastuzumab prescribing information). In our experience, no

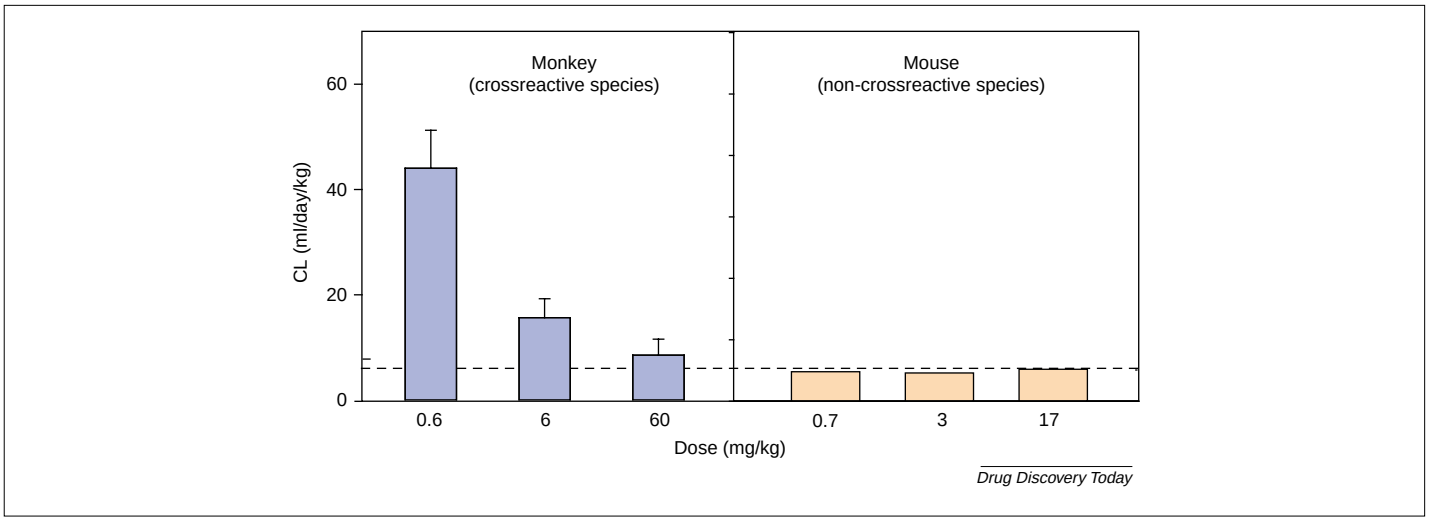

FIGURE 5

Relationship between panitumumab clearance and dose following administration of single intravenous doses in cynomolgus monkeys expressing crossreactive EGFR and mice that express EGFR that is not crossreactive with panitumumab. Single doses of the antibody were administered in monkeys and mice. In monkeys, the columns and bars represent the mean clearance (CL) and the standard deviation, respectively. In mice, the columns represent the clearance (CL) of the antibody at different doses determined from naïve average data collected from mice sacrificed at various time points throughout the study.

impact was observed of age, gender, baseline IgG/IgG2 or rheumatoid factors, baseline serum antigen concentrations and the underlying disease on the clearance of the anti-IL8 IgG2 antibody in a diverse patient population (psoriasis, RA, and COPD) [25]. In psoriasis patients, pharmacokinetic variability in serum exposure to ABX-IL8 following administration of fixed and weight-adjusted doses was similar (the coefficient of variation ranged from 26 to 35%, Figure 6).

Concomitant medications

Xenobiotic metabolizing enzymes, such as cytochrome P450 enzymes, are not involved in elimination of mAbs; therefore, metabolic drug–drug interactions, common for small molecules, are not expected for mAbs. Nevertheless, pharmacokinetic interactions following coadministration of small molecules and mAbs have been documented. Recently, MTX was reported to reduce the apparent clearance of adalimumab (an IgG1 antibody) after single and multiple doses by 29% and 44%, respectively (adalimumab prescribing information). In addition, azathioprine and mycophenolate mofetil were reported to reduce clearance of basiliximab (IgG1) by an average 22% and 51%, respectively (basiliximab prescribing information). Paclitaxel administered with trastuzumab showed to increase concentrations of trastuzumab by 1.5 fold, as compared with serum concentrations of trastuzumab used in combination with anthracycline plus cyclophosphamide (trastuzumab prescribing information). These interactions could be partially caused by the impact of the small molecule drug on the expression of Fcγ receptors or the modulation of the interaction of mAb with the Fcγ receptors on the cells of the effector system. For example, MTX was reported to impact the expression profile of CD64 (FcγRI) on monocytes significantly in RA patients [48]. These co-medications might also affect the immunogenicity of murine protein present in these humanized and chimeric mAbs. It is interesting to note that no impact of MTX administration was observed in the steady-state clearance of ABX-IL8, a fully-human IgG2 antibody, in patients with RA (207 ± 71 ml/day) as compared with the clearance observed in the absence of MTX in psoriasis or COPD patients (226 ± 88 ml/day). These results might be consistent with lower affinity of interaction of IgG2 antibodies with the Fcγ receptors (see Section 'constant region: interaction with Fc receptors') as compared with IgG1 isotype or lack of immunogenicity of the fully-human ABX-IL8 antibody.

Immunogenicity

Immunogenicity of therapeutic antibodies can be a significant problem in the therapeutic use of mAbs containing xenogeneic protein sequences. All currently marketed mAbs have exhibited some level of immunogenicity. In general, murine antibodies have been shown to be more immunogenic and the development of chimeric, humanized, and fully human mAb technology has decreased the immunogenicity of therapeutic mAbs. The immunogenicity profiles of therapeutic mAbs have been addressed in detail in a recent review [49].

Many factors can influence the generation of antiglobulin response following mAb therapy [49,50]. These factors could be related to antibody structure and composition, patient's immune status, concomitant medications, dose formulation and antigen properties [49,50]. Although evolution in generation of mAbs (i.e. moving away from murine antibodies towards humanized or human antibodies) has been crucial in reducing the immunogenicity profiles of the marketed mAbs, the antibody response to therapeutic antibodies still have clinical relevance. For example, the incidence of immunogenicity with adalimumab, a fully human IgG1 antibody generated by phage display technology, has been reported to be 12% when administered as monotherapy [49].

Anti-antibody responses against mAbs can alter pharmacokinetics by impacting clearance, reduce efficacy (anti-idiotypic neutralizing antibodies) and introduce serious safety concerns [2,49]. Immune complex formation in serum has been shown to accelerate clearance of mAbs by the RES. In mice, anti-idiotypic antibodies were shown to increase the clearance of a radiolabeled mAb (TS1) in a dose-dependent way through formation of tetrameric and hexameric

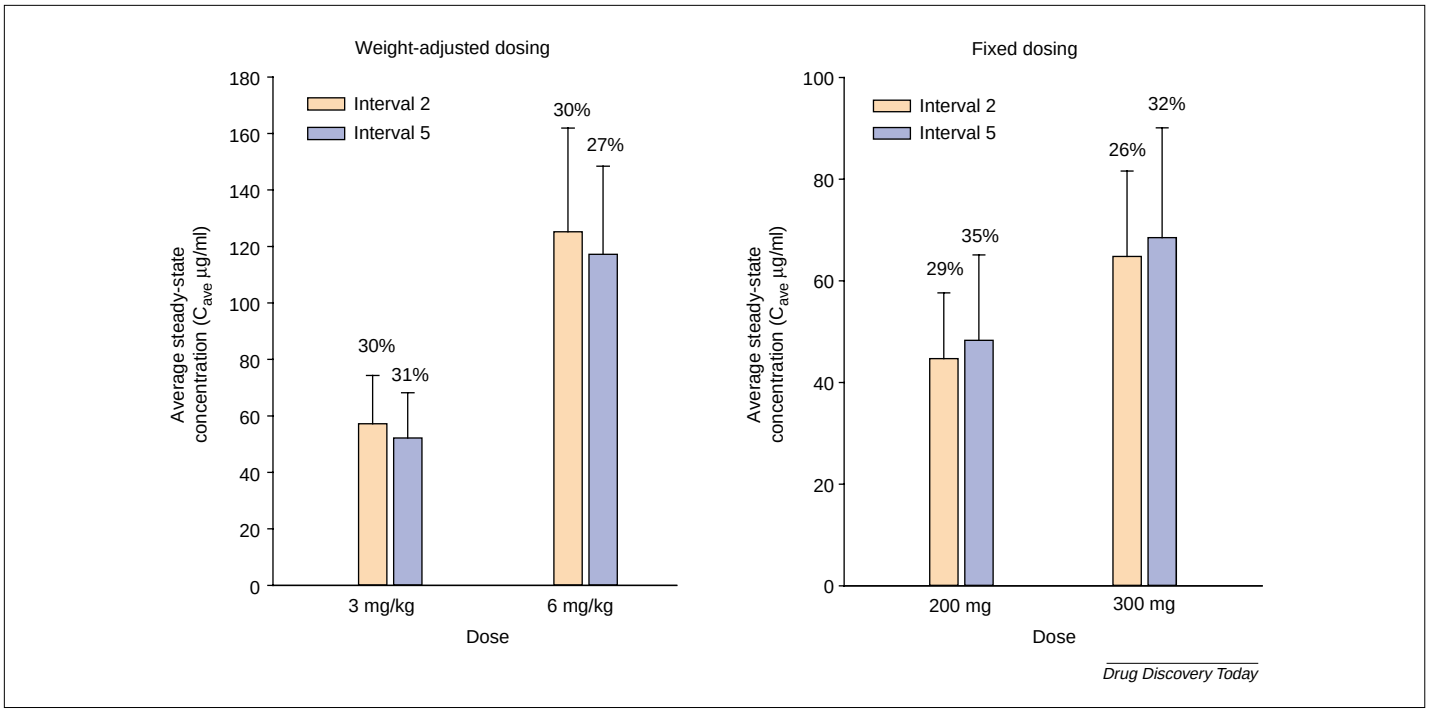

FIGURE 6

Pharmacokinetic variability for ABX-IL8 (anti-IL8 IgG_2 fully human antibody) at steady-state following administration of fixed and weight-adjusted doses. The number indicates the coefficient of variation for each group. The pharmacokinetic variability in serum exposure to ABX-IL8 following administration of fixed and weight-adjusted doses was comparable in patients with psoriasis. The average steady-state concentration (C_{ave}) of ABX-IL8 in serum was calculated over the second (orange) and fifth (blue) dosing intervals.

rings in serum that were primarily cleared by the liver [51]. Clinically, accelerated clearance of infliximab and adalimumab has also been reported, following development of antiglobulin responses in RA patients ([52] and adalimumab prescribing information). Alteration in mAb PK because of the formation of antiglobulin response along with neutralization of antigen binding domain could result in loss of efficacy and hinder repeated mAb administration. Antiglobulin responses to infliximab and OKT®3 have been shown to impact the duration and the extent of the response in patients [52–55]. Serious adverse events and safety risks, such as hypersensitivity reactions, infusion reactions, anaphylactoid reactions, have been associated with immunogenicity of mAb therapeutics [49,52–55].

Future prospects

The number of approved mAbs is expected to increase during the next five years. Advances in innovative technologies and a diversity of novel and validated therapeutic targets will provide many future opportunities for the clinical development of novel mAb-based therapeutics. With further validation of novel targets, new and interesting challenges will be encountered, related to antibody, antigen and host factors. Understanding the factors that impact pharmacokinetics and pharmacodynamics of mAbs is crucial for the therapeutic applications of mAbs and will influence development timelines and improve success probabilities for these novel therapeutic agents.

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