



Review article

Monoclonal antibodies for severe asthma: Pharmacokinetic profiles

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Several monoclonal antibodies (mAbs) (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) are currently approved for the treatment of severe asthma. They have complex pharmacokinetic profiles. These profiles are unique in that they are dependent on their structure as well as can be markedly influenced by the biology of their target antigen, but their general behaviour can still be considered a class property, similar to their endogenous IgG counterpart. They cannot be administered by oral route, have a slow distribution into tissue, are metabolized to peptides and amino acids in several tissues but are protected from degradation by binding to protective receptors (the FcRn), which explains their long elimination half-lives. Their clearance is nonlinear because of the saturation of the target-mediated elimination. Also anti-drug antibody (ADA) response and off-target binding, as well as their glycosylation pattern, can influence the pharmacokinetics of mAbs.

1. Introduction

At the end of the nineteenth century, Paul Erlich understood the importance of using monoclonal antibodies (mAbs) in therapy [1], but only in 1975 the production of mAbs was made possible by the technological innovation of hybridoma developed by Köhler and Milstein [2].

The use of mAbs has expanded exponentially during the last decade and currently covers several therapeutic areas as these drugs offer numerous advantages compared to conventional drugs. In fact, mAbs have a high affinity for, and specificity of, the target, are relatively stable, therefore with a long elimination half-life ($T_{1/2}$) (from weeks to months) and, furthermore, being degraded to amino acids, do not give rise to toxic metabolites.

All mAbs entered into the therapeutic armamentarium share the same basic structure of the immunoglobulins G (IgG) [3]. They are heterodimeric protein molecules with a high molecular weight (150 kDa) consisting of four polypeptide chains, two with identical heavy chains (50 kDa) and two with identical light chains (25 kDa) [4,5]. The heavy and light chains are held together by disulphide bonds to form a Y shape consisting of constant domains (C_H and C_L) and variable domains (V_H and V_L). The light chain contains one constant

domain, C_L . The heavy chain contains three constant domains, C_{H1} , C_{H2} , and C_{H3} . The neonatal fragment crystallisable (Fc) region in the C_{H2} and C_{H3} domains can bind several cell surface receptors, such as the Fcγ receptors (FcγRs) and the neonatal Fc receptor (FcRn), also known as the Brambell receptor, present on the immune effector cells, as well as components of the complement system (i.e., complement C1q) [4]. In humans, three classes of FcγRs, FcγRI, FcγRII, and FcγRIII, have been described [5]. FcγRI is the high-affinity IgG receptor, with $\sim 10^{-8}$ M dissociation constants. FcγRII and RIII display intermediate to low affinities to IgG [6]. FcRn is ubiquitously expressed in both parenchymal (endothelial, epithelial) and hematopoietic cells. Therefore, it is also detectable on monocyte cell surfaces, tissue macrophages and dendritic cells [7].

There are four IgG subclasses: IgG1, IgG2, IgG3, and IgG4. Currently, marketed mAbs are predominantly IgG1, with a lesser degree of IgG2, IgG4 and murine IgG2a isotypes [8]. The preference of this subclass over the others is at least in part determined by the presence of effector functions, such as antibody-dependent cell cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity (CDC), which are important when considering the antireceptor antibodies, which mediate their biological activities by binding to the receptor, without inducing activation, and then act to

Abbreviations: ADA, anti-drug antibody; ADCC, antibody-dependent cell cytotoxicity; AUC, area under the serum concentration; CDC, complement-dependent cytotoxicity; CL, clearance; Cmax, maximum plasma concentration; CRCL, creatinine clearance; eGFR, estimated glomerular filtration rate; F, bioavailability; Fc, neonatal fragment crystallisable; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; IL-5, interleukin-5; IL-5R, IL-5 receptor; mAbs, monoclonal antibodies; Tmax, time to maximum concentration; $T_{1/2}$, elimination half-life; Vd, volume of distribution

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prevent binding of the natural ligand [9], and the consequent effective depletion of eosinophils [10]. Also, high serum levels of IgG1, and manufacturing/stability issues affecting other Ig classes are characteristics that explain why most of the therapeutic Abs on the market are IgG1 [11]. IgG binding affinities vary considerably among FcγRs. IgG1 bind to all human FcγRs, whereas IgG4 bind to FcγRI, FcγRIIA, IIB and IIC and IgG₂ has the lowest affinity for FcγRs [6]. However, it is FcRn that is responsible for the prolonged half-life of IgG antibodies. Antibodies engineered with increased affinity for FcRn, aimed to increase the half-life of IgG for increased bioavailability of therapeutic antibodies, may eventually lead to IgG molecules with increased half-life, but these may come at a cost because they have mutations that are not naturally occurring and may have immunogenicity issues [12].

All antibodies currently available for allergic disorders are humanized or fully human IgG antibodies [9]. The first mAbs that entered therapy were murine (derived from only mouse), but their high immunogenicity has limited their use. The recombinant DNA techniques have allowed replacing the murine sequences with their human counterpart, leading to chimeric antibodies (murine variable part, human constant part) that still carry the risk of development of antimurine Abs, then humanized (human antibody with xenogenic complement determining regions) that use the human Fc and human Fab framework regions but retain murine amino acids in their cytokine-binding complementarity-determining regions and, therefore, could have a remaining tendency to develop antimurine Abs, and finally fully human mAbs [9,11]. Although it is believed that the reduction and ultimately complete removal of murine components from mAbs would result in better tolerability and less or no immunogenic reactivity, immunogenicity of mAb products does seem to be affected by factors beyond the content of murine structures in the mAb molecule [4].

The mAbs currently approved for the treatment of severe asthma are omalizumab that is an anti-IgE agent [13], mepolizumab [14] and reslizumab [15] that bind directly to interleukin (IL)-5 and prevent its link with IL-5 receptor (IL-5R), benralizumab [16] that binds to the α subunit of IL-5R on eosinophils and basophils, thus preventing IL-5 binding and amplifying the ADCC function of these cells by activating natural killer cells to perform apoptosis, and dupilumab [17] that has been specifically designed to inhibit signaling of IL-4 and IL-13.

2. General concept of pharmacokinetics of mAbs

The pharmacokinetics, branch of pharmacology, studies the movement of drugs into, through and out of a living organism from the time of administration until its elimination and is, therefore, described by the time course of the concentration of the specific drug (and its metabolites) in the body [18]. It may be divided into four basic processes, sometimes referred to collectively as 'ADME': absorption, distribution, metabolism, and excretion.

Pharmacokinetics, which are nonspecific general processes, has no correlation with pharmacodynamics aspects, which are determined by activities such as drug-receptor interaction that are specific to drug or drug class [18]. However, the pharmacokinetic processes affect the amount of active drug that reaches intact the target of action and, therefore, influences its activity [18]. In fact, the concentration of drug at the proximity of the biological receptor determines the magnitude of the observed pharmacological responses.

However, when it comes to discussing the pharmacokinetics of mAbs, a fundamental premise is absolutely necessary [19]. Measurement of mAb levels is technically very challenging. This is due to the fact that the equilibrium of free/complexed drug can be significantly altered by the choice of assay format, reagents and conditions, which can in turn impact the interpretation of the pharmacokinetics of the mAb, depending on what drug species is being detected. Therefore, understanding the assay as well as the strengths and limitations of the resulting data are crucial for their interpretation and to draw accurate conclusions.

2.1. Absorption

Absorption is the step through which a drug passes from the administration site to the circulatory stream [18]. At least if not administered intravenously or intra-arterially, a drug must cross one or more membranes in its movement from the site of administration to the general circulation [18]. The ability of drugs to cross the physiological barriers underlies each kinetic stage. Cell membranes form a barrier between the aqueous compartments of the living organism. A single membrane layer separates the extra and intracellular compartments. Conventional drugs can pass these structures by means of passive diffusion through the lipid layer, diffusion through pores or ion channels, carrier-mediated processes, pinocytosis or endocytosis.

Unlike conventional drugs for which all routes of administration can be used, mAbs can be administered exclusively via artificial routes (intravenous, subcutaneous, or intramuscular), because they undergo a rapid proteolytic cleavage at the gastrointestinal level, or denaturation in the acid pH of the stomach if given orally [20] and, furthermore, they have limited intestinal permeability due to their poor lipophilicity, high polarity and large molecular weight [21]. Intravenous and subcutaneous routes are those most frequently used to administer mAbs.

Drugs administered intravenously do not undergo absorption and presystemic metabolism, and therefore the entire dose reaches the general circulation intact [18]. The intravenous administration is usually given as an infusion rather than a bolus, and thus requires dilution of the mAb formulation, including excipients into appropriate fluids suitable for intravenous administration [22]. The intravenous route causes a high initial plasma concentration. Only a drug administered intravenously is 100% bioavailable. Bioavailability (F) is the fraction of the dose administered that reaches the systemic circulation unchanged [23].

The subcutaneous route allows slower absorption. In fact, when given by this route, the mAbs, being large protein molecules (~150 kDa), do not pass into the blood capillaries but they are taken up by lymphatic capillaries and lymph nodes thanks to an absorption process that relies significantly on convection and transcytosis of the mAb through the interstitial space into the lymphatic system and then they eventually enter the blood circulation via the thoracic duct [24]. Compared with blood capillaries, the lymphatic capillaries have a higher permeability for large molecules due to the absence of a well-defined basement membrane and the presence of clefts between the endothelial cells [25]. The subcutaneous route offers an extra benefit since the drug therapy can be targeted to the lymphatic system, which is of particular relevance for agents whose therapeutic targets are lymphoid cells, like interferons and interleukins [26]. The absorption of mAbs usually takes place within hours or days because lymph fluid drains slowly into the vascular system [27].

The subcutaneous absorption can be reduced by presystemic elimination that depends on some factors such as the activity of soluble peptidases present in the interstitial space, the endothelial endocytosis of the cells lining the lymphatic vessels and subsequent lysosomal degradation of the mAbs, the interaction with the phagocytic immune cells in the lymph nodes and the inactivation by the immune system due to the presence of antibodies against mAbs [4]. Moreover, partly because of the limited lymph flow rate in humans (~120 mL/h), mAb absorption from the subcutaneous route is slow, with peak concentrations occurring approximately 6–9 days after administration [3]. It has been suggested that lymphatic flow rate is the most influential factor to time to maximum concentration (T_{max}) [28].

Although several studies have demonstrated that the anatomical site of subcutaneous administration can influence both rate of absorption and bioavailability, there is no consensus for an optimal injection site [29].

In general, the bioavailability of mAbs after a subcutaneous administration is incomplete because of presystemic catabolism at subcutaneous administration site and/or systemic catabolism in draining

lymphatics and blood vessels [30]. Variability between patients related to the subcutaneous layer morphology, the depth of the injections, molecular properties of the mAbs, stability of the mAbs, and mAb formulation are other cited factors that govern the bioavailability of mAbs when they are administered subcutaneously [31].

2.2. Distribution

Distribution is the process by which the drug is transferred reversibly from the general circulation into the tissues as the concentrations in blood increase, and then returns from the tissues into blood when the blood concentrations decrease [18].

Once the systemic circulation is reached, a drug is transported to the various organs and tissues. Carried by the blood, the drugs are distributed in the organism locating inside the cells of the various tissues, in the interstitial fluids that are continually renewed between cell and cell, and in transcellular fluids such as gastric and intestinal fluids.

Tissue distribution of mAbs is governed by a myriad of factors related to the antibody molecular structure, vascular endothelium, fluid flow rates, interaction with target, and interaction with Fc receptors but, due to their large molecular size and physicochemical properties, mAbs do not easily cross the membranes by passive diffusion according to concentration gradient [32] and distribute only to a small extent to target tissues [33]. Therefore, their passage through the biological membranes happens mainly by convection and transcytosis [34].

The underlying principle of the convection is that the difference between the hydrostatic and oncotic pressure (colloidal osmosis), combined with the sieving effect, contributes to the force that moves the mAbs from one side to the other of the membrane. Contrary to the passive diffusion proportional to the concentration, the convection depends on the pressure gradient (hydrostatic pressure-osmotic pressure) between the vascular and interstitial compartments. Transcytosis through vascular epithelial cells (also known as cytopempsis), mediated by FcRn may be another important modality by which mAbs move from the vascular bed to the tissues [35]. When interacting with IgG, FcRn causes its return to the systemic circulation, avoiding the rapid lysosome-mediated degradation of mAb. Macromolecules are captured in vesicles on one side of the cell, drawn across the cell, and ejected on the other side.

Convective transport through paracellular pores is considered to be the primary mechanism of mAb extravasation in tissues. It is driven by the hydrostatic pressure gradient between the blood stream and tissue, and is dependent on the gradient of osmotic pressure and characteristics of the capillary endothelium (nature of the paracellular pores, such as diameter, tortuosity, etc.) and the underlying structure of the basal membrane [18,33]. Obviously, if the pore size is larger the restriction for convective transport is lower [33]. Once the mAbs are inside the cells, they undergo the FcRn recycling pathway, which either transports mAbs to the interstitial spaces or back to the vascular space [36].

The passage of drugs from the blood to the tissues is obviously related to the vascular permeability correlated to the characteristics of the capillary endothelium and to the underlying structure of the basal membrane. In general, there are four types of blood capillaries that could facilitate vascular transport of macromolecules such as mAbs [37]: the sinusoids with fenestrae of about 100 nm present in organs like liver, spleen and tissues such as bone marrow; fenestrated capillaries present in the gastrointestinal tract, in the glands and in the renal glomeruli; continuous capillaries present in the connective tissue, in the skin and in the muscles; finally, in the brain, the capillary endothelium and the underlying structure of the basement membrane are present narrow-junction capillaries. mAbs can be easily distributed in tissues with sinusoids such as the liver or spleen, less in striated muscles, in the skin or in the connective tissue, while they do not pass in any way the blood-brain barrier [8].

Due to its low diffusion capacity, the concentration of mAbs in the interstitial fluid while in their steady-state is much lower than in the

circulation, therefore its volume of distribution (V_d) is relatively low, almost equal to the plasma volume, regardless of the dose used [38]. The distribution is described by the apparent V_d which represents the ratio between the plasma concentration and the dose administered at time 0; therefore, it is expressed in litres/kg of body weight and allows to establish if a drug is relegated to the circulatory stream only, or in interstitial fluids, or spreads throughout the body. It is said to be apparent because it designates the volume of plasma that would be needed to contain the entire drug present in the organism in order to reflect the drug concentration attained in plasma. Some drugs have a V_d similar to that of blood plasma (approximately 0.05 L/kg), intracellular water (about 0.2 L/kg) or total water (approximately 0.55 L/kg). Drugs with high V_d are distributed in all tissues, including the central nervous system; drugs with V_d similar to the plasma, will remain relegated to the circulatory stream. V_d of mAbs is predicted to be relatively small, and it approximately equals the plasma volume, independently of the dose utilized [39].

After extravasation, antibody distribution through the interstitial space relies also upon affinity to target antigens within the interstitial space or on cell surfaces in the tissues. In cases in which there is no target antigen for the mAb to bind (such as in preclinical mouse studies with a human mAb that is not cross-reactive to the murine analogue of its target antigen) or the target is in the plasma, the distribution of the mAb is expected to be limited [4].

The extracellular matrix further hampers the tissue distribution of mAbs [4]. The interstitial space is filled with an extracellular matrix, which has a gelatinous consistency with a negative net charge and is predominantly composed of glycosaminoglycans (e.g. hyaluronic acid) and structural proteins, such as collagen. There is a mutual exclusion between the IgG molecules and the structural proteins of the extracellular matrix. The fraction of the extracellular matrix that is not available for distribution is expressed as the excluded volume. It depends on the molecular weight and the charge of the macromolecule and further limits the extravascular distribution for the mAbs. The excluded volume for IgG molecules was reported as 50% in muscles and skin tissue [4].

The mAbs have a pulmonary distribution that correlates with the plasma concentrations. In cynomolgus monkeys, dose-dependent increases in concentrations of mepolizumab, an IgG1 antibody, have been observed in bronchoalveolar lavage fluid and reported between about 500 and 1,000 times lower than the steady-state plasma concentrations of the antibody [40].

2.3. Metabolism and elimination

The pathways of antibody elimination differ from small molecule drugs in that they are not typically eliminated by renal filtration or by Phase I/II metabolism mediated by enzymes such as cytochrome P450s (CYP450s). Instead, antibodies are mainly eliminated via catabolism following endocytosis and transport to the lysosome [41].

The hepatic elimination of IgG includes degradation in the reticuloendothelial system, which consists of phagocytic cells, such as macrophages and monocytes, and endothelial cells [42]. mAbs are degraded into peptides and amino acids by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue. Actually, metabolism of endogenous IgG is not limited to a specific organ but occurs throughout the body, in those organs and tissues rich in capillary beds with endothelial cells. The contribution of different organs to mAbs catabolism is estimated to be 24%, 16%, 33%, and 12% respectively for skin, muscle, liver and intestine [43]. Therefore, changes in hepatic function are unlikely to have any effect on the elimination of mAbs.

A protective mechanism for IgG molecules, necessary to maintain their plasma concentrations in order to support their physiological function, consists in the recycling of IgG, and therefore mAbs. As already mentioned, mAbs have a Fc region that protects them from

systemic catabolism by binding to FcRn localized in endosomes present in endothelial cells, which may also explain their long $T_{1/2}$. At physiological pH, FcRn has low affinity for IgG, but when the endosome is acidified, the affinity of FcRn increases and allows IgG to attach to it via a specific binding site present in the Fc domain [4]. Once bound, the FcRn-IgG complex is returned to the cell surface to release the IgG molecule from the binding once the physiological pH has been reached. The proteins of the endosomes that are not related to FcRn and recycled undergo a proteolytic degradation in the lysosome. The recycling of FcRn-mediated IgG molecules, including therapeutic mAbs, protects about two-thirds of the IgG molecules assumed in endosomes from catabolic degradation [4].

Together with metabolism, excretion represents the process that frees a living organism from a substance introduced into it. Both processes are described by $T_{1/2}$ and clearance (CL), which are two pharmacokinetic parameters.

$T_{1/2}$ represents the necessary and constant time for the maximum plasma concentration (C_{max}) to be reduced by 50% via different elimination mechanisms; this time for a kinetic process of order 0 is constant. $T_{1/2}$ can be used to make decisions about drug dosage. $T_{1/2}$ of murine IgG is 1–2 days, very short in comparison with human IgG. This is largely due to the low affinity of the former for FcRn. In general, the $T_{1/2}$ of mAbs increases from murine (2–3 days) and chimeric (8–10 days) to humanized or fully human antibodies (20–30 days) [38], which is substantially longer than the $T_{1/2}$ of other proteins with a similar molecular weight [4].

CL is defined as the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion. Therefore, CL of a drug is the factor that predicts the rate of elimination in relation to the drug concentration.

In general, the majority of mAbs show a pharmacokinetic profile characterized by a linear two-compartment model with a rapid clearance phase, with a short distribution process followed by a slower elimination process mediated by a non-specific reticuloendothelial system-dependent clearance and the interaction with FcRn [38]. In FcRn-protected elimination, FcRns are saturated by high IgG concentrations due to limited number of FcRn [44]. In any case, mAbs clearance is a concentration-dependent process, often being a saturable process that depends, to a large extent, on receptor expression (which is usually limited) [4,38]. The number of receptors within the mAbs distribution space affects clearance of mAbs in target-mediated elimination [44]. The affinity of the mAb for the receptor, the dose of the mAb, the rate of receptor-therapeutic protein internalization, and the rate of catabolism within the target cell also influence the rate of elimination of a mAb [4]. Furthermore, presystemic elimination due to degradation at the injection site by proteolytic enzymes when administered by subcutaneous route can influence CL of a mAb [40]. Another form of presystemic elimination is the uptake and processing of protein therapeutics by professional antigen presenting cells in the skin [45].

Also humanized and fully human mAbs can induce endogenous anti-drug antibodies (ADAs) formation. ADAs produce inactive immune complex (mAb-ADAs complex) and, in any case, formation of mAb-ADAs complex accelerates mAbs clearance because binding of the mAb to ADAs triggers lysosomal degradation in the same manner as target-mediated elimination [44].

3. Factors that modify the pharmacokinetics of mAbs

Differences in polysaccharide (glycan) chains may induce pharmacodynamic and pharmacokinetic differences in mAbs [46].

A critical component in the ability of a mAb to induce ADCC or CDC is its affinity with FcγRs and C1q. The Fc region in antibodies is responsible for induction of ADCC via interaction with the FcγRIIIA receptor (CD16) on the surface of immune cells, for example, NK cells, that initiates production of cytotoxic granules, which results in degradation of the target cell membrane [46]. However, other

mononuclear leukocytes (macrophages, γδ T cells) and polymorphonuclear leukocytes (neutrophils, basophils, eosinophils) can both mediate ADCC [47]. Actually, FcγRIIIA cross-linking has also been specifically implicated in cytokine release from adherent human monocytes/macrophages [48,49]. In any case, in humans, also FcγRI (CD64), FcγRIIA and FcγRIIC (CD32) are capable of eliciting ADCC whereas FcγRIIB receptor suppresses ADCC response [50]. Thus the balance between activating and inhibitory signals from the FcγRs is an important determinant for the magnitude of ADCC response. Interaction of the complement C1q system with the antibody Fc fragment initiates a reaction cascade causing the destruction of the target cell membrane [46].

This effect is modulated by glycans in the CH2 domain of the Fc region. The CH2 domain of each heavy chain contains one N-glycosylation site at approximately Asn297 and about one-fifth of human IgGs carry a N-glycosylation motif in the variable region [51]. Sialylation and core fucosylation generally inhibit ADCC, whereas defucosylation results in a significantly enhanced ADCC due to the FcγR IIIA receptor binding affinity.

Glycosylation itself is not required for maintaining IgG's long $T_{1/2}$ [52]. However, terminal mannose or sialic acids can have significant impact on pharmacokinetic of mAb or Fc-fusion proteins. Mannose, especially high mannose variants (Man5/8/9) content in the mAb, can have significant impact on the pharmacokinetic of the molecule, potentially reducing the exposure, leading to lower efficacy. The sialylation level has significant impact on pharmacokinetic of Fc-fusion molecules in that lower sialylation can result in lower exposure [52].

Body weight is a clinically relevant covariant that may modify CL, and V_d whereas age, sex and history of smoking do not have a clear impact on mAb pharmacokinetics [53].

Isoelectric point and local charge patches have been shown to influence mAb disposition, where increase in positive charge of antibodies likely increases CL and distribution due to interactions with negatively charged components on the tissue [54].

mAbs can be recognized after their administration by the patient's immune system with the consequent formation of anti-drug antibodies. The formation of antibodies against biologic agents can lead to the elimination of these through the reticuloendothelial system, so drugs that act on the patient's immune system will also act, indirectly, on the drug's metabolism [55]. Several reports or specific clinical trials have suggested an alteration in the pharmacokinetics of mAbs when these are administered to patients concomitantly with immunosuppressant drugs such as methotrexate, azathioprine and mercaptopurine. Inhibition of the immune system by immunosuppressive drugs can interfere with mAbs clearance by reducing the formation of autoantibodies [20]. However, the effect of the concomitant immunosuppressant drugs on the clearance of mAbs seems to be minimal and probably does not necessitate any dosage adjustments [39].

Small molecule drugs, such as statins and fibrates, may affect the expression of target of some mAbs, such as alirocumab and evolocumab by altering, their target-mediated clearance [20]. Statins and fibrates induce the proprotein convertase subtilisin kexin-like 9 (PCSK9) expression and thus the clearance of alirocumab and evolocumab [56] although this interaction is not considered clinically relevant. PCSK9 is a secreted glycoprotein that is transcriptionally regulated by cholesterol status [20].

However, since CYP450 or drug transporters such as P-glycoprotein do not mediate the metabolism, distribution and elimination of mAbs, mAbs are not expected to compete directly with chemically derived drugs [20], although there is evidence that TNFα, IL-6 and IL-1β are inhibitors of CYP3A4, CYP2B6 and CYP2C8 expression [57], so when TNF-α, IL-6 or IL-1β-inhibiting mAbs are administered, there will be an increase in the expression of these isoforms with the consequent increase in the degradation of the drugs in whose metabolism they are involved [58]. However, since inflammation associated with infection or other disease states down-regulates multiple P450 enzymes and there

is good evidence exists that the pattern of regulation differs depending on the disease, and that proinflammatory cytokines are the principal mediators of these effects, it is not surprising that the effect of onset or amelioration of inflammation on CYP450 expression or activity and, consequently, the effect of anticytokine drugs (including anticytokine mAbs) have been documented [59].

4. The potential role of pulmonary delivery

The systemic route is generally used for the administration of mAbs in humans, but it results in very low concentrations of mAb in the lungs and exposes the rest of the body to potential toxicity and severe adverse effects [60].

The inhalation route is potentially useful because the pulmonary delivery of mAbs might increase their lung exposure and consequently provides a targeted approach for providing mAbs to inhibit cytokine pathways in the lung [61], which could be better when treating a patient suffering from asthma. Compared with subcutaneous administration, inhalation may provide a more rapid onset of action at lower doses than systemic treatments and may be suitable for use in a broader range of patients [62]. It might also reduce the potential for toxicity associated with systemic exposure. In fact, there is evidence that the delivery of mAbs via the airways is practicable, effective, and well tolerated, leading to sustained high levels of accumulation of molecules retaining their physical and immunological properties in the lungs, with only very slow absorption of small quantities of the mAb into the blood circulation [63].

Actually, the development of aerosolized mAbs for pulmonary delivery is a possibility considered with real interest mainly because the lungs have a very large surface area and a high perfusion rate. Nevertheless, the small number of inhaled mAbs may be explained by their instability during aerosolization and the paucity of biological and immunological data on mAbs deposited into the respiratory tract [64].

The fate of drugs after airway-mediated delivery depends on their site of deposition in the lungs [60]. However, the passage into the blood of mAbs delivered via the pulmonary route is poor and slow, with drug bioavailability ranging from about 1 to 10% of the dose inhaled [65]. Given the rate of retention of the macromolecules in the lungs after delivery via the airways, it is crucial to address clearly the pathophysiological mechanisms of action of the antigen and to target only antigens active within the lung to achieve a therapeutic effect [60]. Another consideration regarding the use of mAbs as respired therapeutics is immunogenicity [60]. It has been speculated that inhaling full-length mAbs may be more immunogenic than administering them parentally [66]. However, since aggregated proteins are known to be highly immunogenic, this may be the cause [60]. In fact, the protein aggregates formed in response to various stresses may raise immunogenicity, and prompt the production of potentially neutralizing anti-drug antibodies [67].

In any case, the expression of FcRn by pulmonary epithelial cells is an advantage because it may facilitate efficient systemic absorption of antibody delivered to the lung. However, only small volumes of fluid can be administered and, consequently, just mAbs with very high dose potency are suitable for pulmonary delivery [68].

5. Pharmacokinetic profile of mAbs already approved for the treatment of asthma

Table 1 defines the currently available mAbs approved for the treatment of severe asthma, and Table 2 reports a summary of their pharmacokinetic parameters.

5.1. Omalizumab

Omalizumab is administered subcutaneously every two to four weeks depending on body weight and baseline IgE level of the patient

and its bioavailability is 62% on average [69]. A two-compartment model describes the serum omalizumab concentrations following subcutaneous or intravenous administration of single or multiple doses with a V_d approximating plasma volume [70]. It is slowly absorbed, and serum concentrations peak 7–8 days after administration. The mean C_{max} of omalizumab at steady state was 30.9 mg/L following an initial dosage of 2.0 mg/kg, and 6 subsequent dosages of 1.0 mg/kg administered intravenously over 77 days to adult patients with allergic asthma [71]. Trough concentrations of omalizumab in patients with allergic rhinitis were similar when the drug was administered intravenously or subcutaneously; however, there was a slow absorption phase over several days with peak serum concentrations of > 2 mg/L reached by 14 days after subcutaneous administration of omalizumab 0.15 mg/kg [72]. After multiple doses, the area under the serum concentration (AUC) of omalizumab increases; at a steady state, the AUC over 14 days was up to 6 times that observed after the first dose [73]. Omalizumab is cleared slowly from circulation with a terminal $T_{1/2}$ of 1–4 weeks [70,72,74,75]. Clearance of omalizumab involves IgE clearance processes, which include degradation in the liver reticuloendothelial system and endothelial cells, and clearance via binding and complex formation with IgE at rates that were generally faster than IgG clearance [72]. In asthma patients, the apparent clearance of omalizumab from serum averaged 2.4 mL/kg/day [69,76,77].

When patients received two subcutaneous injections of omalizumab at one of three dosage levels (450, 525, or 600 mg), chosen according to baseline IgE (300–2000 IU/mL) and bodyweight (40–150 kg), with a 14-day interval between injections, serum omalizumab concentrations slowly increased and reached peak values 2–10 days after the first administration, regardless of dosage [78]. Following the second dose on Day 15, omalizumab concentrations increased further and reached overall peak values a couple of days later. The mean terminal $T_{1/2}$ of omalizumab was around 20 days (range of means for the three dose groups: 18–22 days). The mean apparent CL/F of omalizumab was 6.9–9.2 mL/h. Omalizumab total exposure as assessed by AUC from time zero to infinity (AUC_{∞}) was in the same range for the three dose groups.

Pharmacokinetic/pharmacodynamic modeling and simulation, together with pooled analyses of safety data, suggests that those patients currently receiving omalizumab at doses of 225 or 300 mg every 2 weeks are able to switch to omalizumab 450 and 600 mg, respectively, every 4 weeks, without compromising safety or efficacy [79]. Subcutaneous injections of 300 mg every 2 weeks and 600 mg every 4 weeks translate to comparable steady-state concentrations of drug, the same steady-state concentrations of free IgE and the same steady-state downstream effector cell desensitization, and hence the same clinical response.

The pharmacokinetic profile of omalizumab is similar in adults, adolescents and children [75].

Analyses of population pharmacokinetics of omalizumab suggest that no dose adjustments are necessary for the age range 6–76 years, race, ethnicity, gender or Body Mass Index [80]. There are no pharmacokinetic or pharmacodynamic data in patients with renal or hepatic impairment [80].

Aerosolized omalizumab was found to be ineffective in humans [60]. It is likely that the low levels of omalizumab in the serum after airway-mediated delivery are probably insufficient to neutralize serum IgE.

5.2. Mepolizumab

Mepolizumab was first given as a single intravenous infusion at rates of 0.05 mg/kg, 0.5 mg/kg, 2.5 mg/kg, 10 mg/kg, or placebo in men with mild allergic asthma [81]. The drug was found to be quantifiable in full-profile blood samples obtained on the day of the infusion and over the 16-week follow-up period in the majority of patients receiving doses > 0.05 mg/kg. Mepolizumab declined biexponentially

Table 1
Currently available mAbs used against severe asthma.

mAb	Source/manufacturer	Antibody type	Target	Commercial names	Approved
Omalizumab	Novartis, Genentech	Humanized, IgG1	IgE Fc region	Xolair	FDA on June 20, 2003 EMA on October 25, 2005
Mepolizumab	GlaxoSmithKline	Humanized, IgG1/ κ	IL-5	Nucala	FDA on November 4, 2015 EMA on December 1, 2015
Reslizumab	Teva	Humanized, IgG4	IL-5	Cinqair (US), Cinqaero (EU)	FDA on March 23, 2016 EMA on June 23, 2016
Benralizumab	AstraZeneca, Kyowa Hakko Kirin	Humanized, IgG1/ κ	IL-5R (CD125)	Fasenra	FDA on November 14, 2017 EMA on January 8, 2018
Dupilumab	Regeneron, Sanofi Genzyme	Fully human, IgG4	IL-4R α inhibiting the signalling of IL-4 and IL-13	Dupixent	FDA on October 19, 2018 EMA on March 1, 2019

after infusion. The mean $T_{1/2}$ was found to be approximately 2 days and was followed by a terminal $T_{1/2}$ of approximately 20 days (range 14–30 days), which was dose independent. The C_{max} and in the area under the plasma AUC_{∞} demonstrated a dose-proportional relationship, with coefficients of variation generally < 20%. Plasma CL and steady-state volume of distribution were similar across the dose range, indicating linear pharmacokinetic profile.

In a second study, men with mild allergic asthma received a single intravenous infusion of mepolizumab infusion 0.5 mg/kg, 2.5 mg/kg, 10 mg/kg, or placebo [82]. Persistent and dose-dependent relationship was re-demonstrated as already seen in the previously described study. Mepolizumab decreased bi-exponentially according to a two-compartment model. Eosinophil cell count suppression varied among dose groups and was longer lasting in patients receiving either 2.5 or 10 mg/kg of mepolizumab. At 16 weeks post-dose, eosinophil count remained at 8–36% of baseline levels, but closer to baseline or higher than baseline in patients receiving 0.5 mg/kg. The duration of suppression positively correlated with increasing dose, with maximal reduction in eosinophil count occurring at 3–4 days after C_{max} .

Also in healthy Japanese male subjects who received either a single mepolizumab intravenous dose (10, 75, 250, or 750 mg) or placebo, pharmacokinetics showed dose-proportional increases in AUC and C_{max} [83]. However, the $T_{1/2}$ variability was higher at 250 mg (36 days) than at 75 and 750 mg (20 and 23 days, respectively).

In patients with persistent asthma despite inhaled steroid therapy, who received mepolizumab 250 mg, 750 mg or placebo every 4 weeks, the mean plasma mepolizumab concentration was 22.2 ng/ml in the 250 mg dose group and 51.2 ng/ml in the 750 mg dose group [84]. Mepolizumab exhibited approximately dose-proportional pharmacokinetics and a long terminal $T_{1/2}$ of approximately 21 days.

In a phase I study, healthy volunteers were randomly assigned to receive a single dose of either mepolizumab 250 mg by intravenous injection, subcutaneous injection (upper arm, abdomen, or thigh), or intramuscular injection [85]. The mean values of C_{max} were 109 μ g/mL, 34.1–38.2 μ g/mL, and 46.9 μ g/mL following intravenous, subcutaneous and intramuscular administration, respectively. Although the time taken to reach the C_{max} was longer (2–14 days) in the subcutaneous than the intravenous administration, mepolizumab was found to be equally well absorbed in both routes of administrations. The mean AUC_{∞} were 1,557 μ g d/mL, 1,110–1,238 μ g d/mL, and 1,395 μ g d/mL for intravenous, subcutaneous, and intramuscular administration, respectively. Regardless of the route of administration, mepolizumab demonstrated a median terminal $T_{1/2}$ of approximately 20 days (18.5, 17.9–20.4, and 19.2 days following intravenous, subcutaneous and intramuscular administration, respectively). The mean bioavailability for each injection site was 64%, 75%, 71%, and 81% for subcutaneous abdomen, arm, thigh, or intramuscular, respectively.

It has been suggested that a 100 mg subcutaneous dose of mepolizumab should be considered to equate to a 75 mg intravenous dose of the drug, based on the absolute bioavailability of the subcutaneous administration route [86]. In any case, the route of administration does

not affect the mepolizumab exposure eosinophil response relationship [86].

The pharmacokinetics of mepolizumab was also evaluated in a separate multi-dose, double-blind, randomized, placebo-controlled, parallel-group trial in patients with mild asthma [82]. Patients received 250 mg abdominal subcutaneous doses of mepolizumab at weeks 0, 6, and 8. In a period of 24 weeks (16 weeks, after dose 3), mepolizumab was quantifiable in all blood samples obtained. Plasma accumulation after the third dose showed a 65% increase in AUC_{∞} and an 80% increase in C_{max} compared with after the first dose. Mepolizumab had a long $T_{1/2}$ of 20 days and with the difference in administration between dose 1 and 2, and doses 2 and 3, a plasma accumulation was observed after the third dose of the drug. T_{max} and terminal $T_{1/2}$ did not vary from the single-dose administration study group suggesting mepolizumab has a time independent pharmacokinetics.

It has been reported that at steady state, there is approximately two-fold accumulation of mepolizumab, when administered subcutaneously every 4 weeks [86].

In patients with asthma, mepolizumab has an estimated central V_d of 3.6 L in those weighing 70 kg [87].

Proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue degrade mepolizumab, which is a humanized IgG1 mAb [87]. Therefore, it is not expected that hepatic impairment does not affect pharmacokinetics of mepolizumab. Furthermore, having a higher molecular weight, mepolizumab does not undergo renal filtration; consequently, creatinine clearance (CR_{CL}) between 50 and 80 mL/min should not have any impact on its pharmacokinetics, but it must be highlighted that data in patients with CR_{CL} < 50 mL/min are limited.

There are limited pharmacokinetic data available in the paediatric population and in elderly patients (≥ 65 years old) [88]. However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12–82 years.

Gender and race have no significant effect on mepolizumab CL, according to population pharmacokinetic analysis [87].

5.3. Reslizumab

A first human study evaluated the pharmacokinetics of increasing single doses of reslizumab (0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg) administered intravenously in patients with severe persistent asthma [89]. The plasma concentrations of reslizumab were dose proportional. Its mean systemic exposure (AUC) increased in a 1.2–2.5–9.23 proportion as the dose increased in a 1.3–3.3–10–33.3 proportion. The mean C_{max} obtained 6.9 h after reslizumab dosing at 1.0 mg/kg was 30.3 μ g/mL. Mean concentrations were 0.87 μ g/mL on Day 90 and 0.43 μ g/mL on Day 120 after 1.0 mg/kg, suggesting that this could represent a threshold value of biological activity. The elimination $T_{1/2}$ ranged between 24.5 and 30.1 days.

The pharmacokinetic properties of intravenous reslizumab, which

Table 2
Summary of pharmacokinetic parameters of mAbs for severe asthma.

mAb	Dose	Parameters			
		C _{max}	AUC _∞	CL	T _{1/2}
Omalizumab	2 × 450 mg SC	121.9 ± 53.2 µg/mL	4602 ± 944 day·µg/mL	8.49 ± 1.84 mL/h	21.6 ± 2.9 days
	2 × 525 mg SC	161.2 ± 30.4 µg/mL	6666 ± 1570 day·µg/mL	6.90 ± 1.64 mL/h	17.6 ± 3.8 days
	2 × 600 mg SC	148.1 ± 38 µg/mL	5946 ± 1910 day·µg/mL	9.18 ± 2.77 mL/h	18.5 days
Mepolizumab	250 mg IV	109 ± 17 mg/mL	1,557 ± 250 day·µg/mL		17.9–20.4 days
	250 mg SC	34.1–38.2 ± 7.3–12.1 mg/mL	1,110–1,238 ± 228–372 day·µg/mL		19.2 days
Reslizumab	250 mg IM	46.9 ± 10.6 mg/mL	1,395 ± 348 day·µg/mL	≈ 7 mL/h	≈ 24 days
	3.0 mg/kg IV	86.27–105.33 µg/mL	27.2–33.1 mg h/mL		7 ± 2–16 ± 3 days
Benralizumab	0.03–3 mg/kg IV	1 ± 0.3–82 ± 18 µg/mL	5 ± 2–775 ± 110 day·µg/mL	65 ± 28–71 ± 18 mL/kg	
	25–200 mg SC	1.2–14	0.12 ± 0.071–1.2 ± 0.11 day·µg/mL		
Diplumab	600 mg SC	70.1 ± 24.1 µg/mL		0.131 L/day	4.8 ± 1.3 L

AUC_∞: area under the mAb serum concentration from time zero to infinity; CL: systemic clearance; C_{max}: maximum serum concentration; T_{1/2}: elimination half-life; V_d: volume of distribution. Data from Refs. [78,85,93,100,102,103].

were characterized in volunteers (n = 130), patients with asthma (n = 438) or nasal polyps (n = 236), were similar across these subjects, with variability in peak and overall exposure between individuals of about 20–30% [90]. Serum C_{max} usually occurred at the end of the infusion and generally declined from this peak showing a biphasic decrease. The drug accumulates approximately 1.5- to 1.9-fold in the serum following multiple doses and had a V_d of ≈ 5 L, which indicates a minimal distribution to the extravascular tissue, CL of ≈ 7 mL/h, and is expected to be linear and non-target mediated, and T_{1/2} of ≈ 24 days, which suggests minimal distribution to the extravascular tissues. Pharmacokinetics is dose-proportional at doses of 0.3–3.0 mg/kg. A population pharmacokinetic model has recently documented that the overall steady-state exposures of reslizumab after intravenous administration were comparable across a greater than fourfold range of patient body weights (33.9 to < 63 kg, 63 to < 73 kg, 73 to < 85.5 kg, and 85.5–156 kg) [91]. However, in another reslizumab population pharmacokinetic model, heavier body weight was associated with more rapid CL and a larger V_d, supporting the appropriateness of the recommended weight-based dosing (3 mg/kg), which produces comparable exposure across the entire range of weights [92].

Since kidneys and liver are not involved in the disposition of mAbs, hepatic and renal impairments are not likely to alter pharmacokinetics enough to justify dosage adjustment [93]. No substantial differences in pharmacokinetics in patients with mild (estimated glomerular filtration rate [eGFR] of 60–89 mL/min per 1.73 m²) or moderate (eGFR of 30–59 mL/min per 1.73 m²) renal impairment have been observed compared with those having normal renal function [94].

Population pharmacokinetic analyses demonstrated that there was no significant effect of age, race, or gender on the pharmacokinetic of reslizumab [94]. No formal clinical drug interaction studies have been performed with reslizumab.

5.4. Benralizumab

The pharmacokinetic activity of single intravenous ascending dose (0.0003–3 mg/kg) of benralizumab in patients with mild atopic asthma was approximately dose proportional [95]. 3 mg/kg dose produced a C_{max} and AUC_∞ of 82 µg/mL and 775 µg day/mL, respectively. CL was 4 mL/kg/day, V_d at steady state was 71 mL/kg, which was greater than the plasma volume suggesting potential binding of benralizumab to IL-5Rα-expressing blood cells and/or penetration into extravascular tissues, and T_{1/2} was 16 days, which is typical for human IgG antibodies [95].

A Phase II multiple ascending dose (25, 100, or 200 mg) safety study using a subcutaneous formulation of benralizumab in adult asthmatics resulted in pharmacokinetic/pharmacodynamic activities similar to those observed with intravenous dosing [96,97].

Two Phase I trials in Japanese healthy males confirmed the pharmacokinetics of ascending single intravenous (0.03, 0.1, 0.3, 1, or 3 mg/kg) and subcutaneous (25, 100, or 200 mg) doses of benralizumab [98]. Intravenous doses produced dose-proportional increases in serum concentration with biphasic elimination and a T_{1/2} of 10.2–18.7 days. Subcutaneous doses were gradually absorbed, reaching peak concentration in 4–7 days. Serum benralizumab concentrations were approximately dose-proportional and the drug underwent monophasic elimination with a T_{1/2} of between 15.6 and 17.4 days.

Population pharmacokinetic modelling based on data from early-stage studies in volunteers and patients with asthma found that the pharmacokinetic properties of subcutaneously administered benralizumab were dose-proportional and best described by a two-compartment model with first-order absorption and first-order elimination from the central compartment [99]. The absorption of benralizumab from the subcutaneous dosing site was relatively slow, with an estimated absorption rate constant of 0.252 days (mean absorption time of 3.97 days) and bioavailability of 52.6%. Estimated median systemic CL was 0.323 L/day and V_d in the central and peripheral compartments was

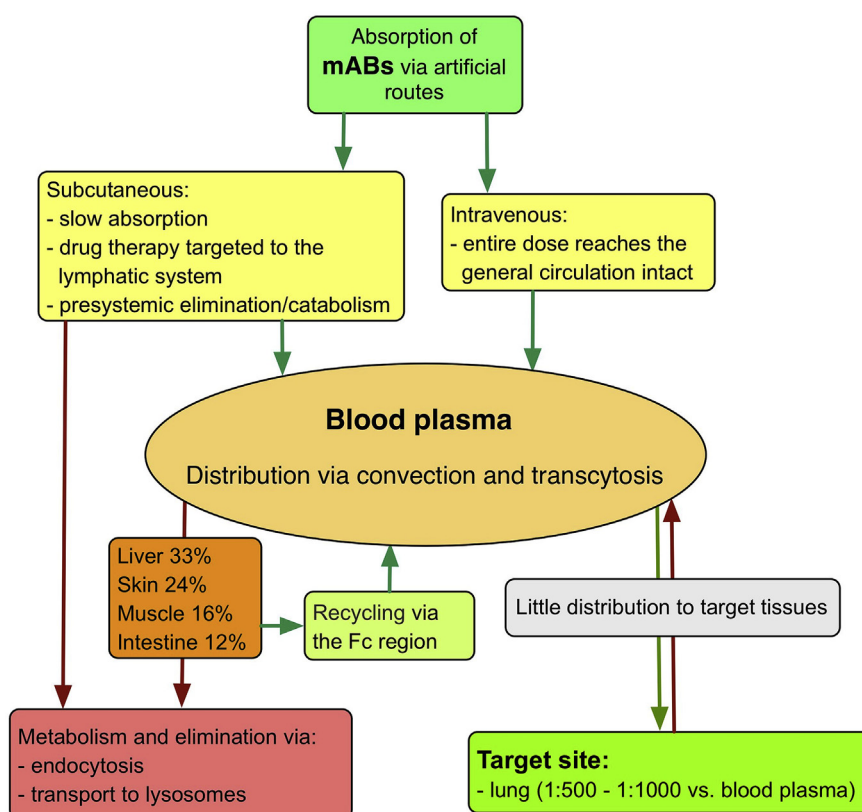


Fig. 1. Pharmacokinetics of mAbs.

3.16 and 2.83 L, respectively, suggesting limited extravascular distribution of benralizumab. In those patients with high ADAs titers (≥ 400), CL of benralizumab was elevated 4.6-fold. Body weight was identified as a clinically relevant covariate affecting systemic CL and V_d of the central and peripheral compartments. Although there was a racial difference in V_d of the central compartment, this was not considered clinically relevant. Age, sex, and tobacco smoking history had no apparent impact on the pharmacokinetic of benralizumab in healthy volunteers or patients with asthma.

It must be mentioned that benralizumab is a fully humanized afucosylated IgG1κ mAb. Afucosylation enhances its interaction with its binding site and, consequently, influences its pharmacokinetic profile [100].

5.5. Dupilumab

Subcutaneous dupilumab exhibits non-linear target-mediated pharmacokinetics [101,102], with greater than dose proportional increases in exposure (an eightfold dose increase from 75 to 600 mg produced a 30-fold increase in systemic exposure) [101]. Following an initial subcutaneous dose of 600 mg, dupilumab reaches a C_{max} of 70.1 µg/mL by approximately one week after the dose [103]. Steady-state concentrations are achieved by week 16 following the administration of 600 mg as an initial dose and 300 mg either every other week or weekly. Across clinical trials, the mean steady-state trough concentrations ranged from 73.3 µg/mL to 79.9 µg/mL for 300 mg administered every 2 weeks and from 173 µg/mL to 193 µg/mL for 300 mg administered weekly [103]. Subcutaneous dupilumab has an estimated bioavailability of about 64% [101,103]. Dupilumab reaches non-detectable concentrations in 13 and 10 weeks, respectively, with regimens of 300 mg once weekly and once every 2 weeks. The estimated total V_d is about 4.8 L. According to data from phase III trials in patients with moderate-to-severe atopic dermatitis, there were no time-dependent changes in the pharmacokinetics of dupilumab during

longer-term (up to 68 weeks) treatment [104].

Dupilumab trough concentrations are lower in subjects with higher body weight [103], but dosage adjustment based on body weight does not appear to be necessary in adults [102]. Gender and age do not appear to affect dupilumab pharmacokinetics to a clinically relevant extent [101,105]. The effect of hepatic or renal impairment on dupilumab pharmacokinetics has not been studied; however, dupilumab is not expected to undergo significant hepatic or renal elimination.

A population pharmacokinetic analysis of dupilumab in adult and adolescent patients with asthma has determined that the pharmacokinetic of dupilumab in asthma patients were adequately described by a 2-compartment with parallel linear and nonlinear saturable Michaelis-Menten elimination model plus first-order absorption [106]. The estimates of the key pharmacokinetic parameters were: V_d at steady-state 4.37 L, linear elimination rate 0.042 day⁻¹, and bioavailability 60.9%. Excluding the body weight, all other covariates examined, such as age (12–83 years), gender, race, laboratory parameters of liver function, biomarkers/disease characteristics (eosinophils, FeNO, and FEV₁%), and population had no statistically significant effect on dupilumab pharmacokinetics.

6. Conclusion

The mAbs are a unique class of therapies that show a pharmacokinetic behaviour that are influenced and controlled by the specific mechanisms and processes involved in their disposal (Fig. 1). Although there are substantial differences in pharmacokinetic of individual mAbs, their general behaviour can still be considered a class property, similar to their endogenous IgG counterpart. The mAb pharmacokinetic properties, however, can be further modulated by several factors.

In any case, although great progresses have been made in improving our understanding of the pharmacokinetics of mAbs and factors that impact them, there are still many unresolved questions such as causes influencing subcutaneous bioavailability, clear role of Fc receptors in

efficacy and biodistribution, prediction of immunogenicity, and influence of molecular properties such as charge, hydrophobicity, glycosylation, and their interdependencies. Furthermore, the potential for drug-drug interactions with these mAbs is classified as low by regulatory agencies in consideration of their target, elimination mechanism, favourable safety profile and the lack of mechanism of action rationale for a potential interaction. No drug interaction studies have therefore been conducted.

However, asthma patients are commonly treated with exogenous corticosteroids. Corticosteroids are metabolized in the lung and liver by members of the cytochrome P450 (P450) CYP3A family of enzymes [107]. Considering the anti-inflammatory effect of anticytokine drugs (including anticytokine mAbs), which certainly leads to amelioration of inflammation and, consequently, an improvement in the activity of CYP enzymes [59], it is worth investigating if such patients have better tolerance and/or longer efficacy of therapeutic mAbs.

Conflict of interest

Maria Gabriella Matera, Luigino Calzetta, Paola Rogliani, and Mario Cazzola have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript, including employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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