



HAL
open science

Influence of Antigen Mass on the Pharmacokinetics of Therapeutic Antibodies in Humans

David Ternant, Nicolas Azzopardi, William Raoul, Theodora Bejan-Angoulvant, Gilles Paintaud

► **To cite this version:**

David Ternant, Nicolas Azzopardi, William Raoul, Theodora Bejan-Angoulvant, Gilles Paintaud. Influence of Antigen Mass on the Pharmacokinetics of Therapeutic Antibodies in Humans. *Clinical Pharmacokinetics*, In press, 10.1007/s40262-018-0680-3 . hal-01821717

HAL Id: hal-01821717

<https://hal.science/hal-01821717v1>

Submitted on 7 Sep 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Influence of antigen mass on the pharmacokinetics of therapeutic antibodies in humans

David Ternant^{1,2}, Nicolas Azzopardi¹, William Raoul¹, Theodora Bejan-Angoulvant^{1,2}, Gilles Paintaud^{1,2}

¹Université de Tours, EA7501 GICC, team PATCH, Tours, France

²CHRU de Tours, Department of medical pharmacology, Tours, France

Corresponding author

David Ternant
Tours university hospital
Department of medical pharmacology
2 boulevard Tonnellé
37044 TOURS Cedex
France
Tel: +33247476008
Fax : +33247476011

Short title: antigen mass and antibody pharmacokinetics

Abstract word count: 219/250

Manuscript word count: 5997/6000

Number of tables: 3

Number of figures: 3

Abstract

Therapeutic antibodies are increasingly used to treat various diseases, including neoplasms and chronic inflammatory diseases. Antibodies exhibit complex pharmacokinetic properties, notably due to the influence of antigen mass, i.e. the amount of antigenic targets to which the monoclonal antibody binds specifically. This review focuses on the influence of antigen mass on the pharmacokinetics of therapeutic antibodies quantified by pharmacokinetic modelling in humans. Out of 159 pharmacokinetic studies, 85 reported an influence of antigen mass. This influence led to nonlinear elimination decay in 50 publications which was described using target-mediated drug disposition (TMDD) or derived models, as quasi-steady-state, irreversible binding and Michaelis-Menten models. In 35 publications, the pharmacokinetics was apparently linear and the influence of antigen mass was described as covariate of pharmacokinetic parameters. If some reported covariates, such as circulating antigen concentration or tumor size, are likely to be correlated to antigen mass, others, such as disease activity or disease type, may contain little information on the amount of antigenic targets. In some cases, antigen targets exist in different forms, notably in the circulation and expressed at cell surface. The influence of antigen mass should be soundly described during the early clinical phases of drug development. To maximize therapeutic efficacy, sufficient antibody doses should be administered to ensure the saturation of antigen targets by therapeutic antibody in all patients. If necessary, antigen mass should be taken into account in routine clinical practice.

Key points

- Current knowledge on the pharmacokinetics of monoclonal antibodies (mAbs) states that higher antigen amount was associated with mAb concentrations and higher mAb clearance.
- Because of antigen mass, mAb pharmacokinetics may display nonlinear elimination shape. The influence of antigen mass on mAb pharmacokinetics is described using target-mediated drug disposition (TMDD) model, or approximations of this model. Antigen mass influence may be quantified using covariates.
- Current mAb clinical development and use in clinical practice may be improved by optimization of dose, which should ensure the saturation of antigen targets in all patients.

Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
AS	Ankylosing spondylitis
CD	Crohn's disease
CDX	Cluster of differentiation X
CEA	carcino-embryonic antigen
CLL	Chronic lymphocytic leukemia
CRP	C-reactive protein
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
ECOG	Eastern cooperative oncology group
ELISA	Enzyme-linked immunosorbent assay
Fab	Antigen binding portion
Fc	Crystallizable portion
FCGRA	Gene encoding Fc γ RIIIA
FcRn	Neonates Fc portion receptor
Fc γ R	receptor of Fc portion of IgG
GPIIb/IIIa	Glycoprotein IIb/IIIa
HBI	Harvey-Bradshaw index
HER, EGFR	Human epidermal growth factor receptors
HER2-ECD	Extracellular domain of human epidermal growth factor receptor 2
HPLC-MS/MS	High pressure liquid chromatography coupled with tandem mass spectrometry
IBD	Inflammatory bowel disease
IgG	Immunoglobulin of isotype G
IL-X	Interleukin X
IL-XR	Receptor of interleukin X
IM	Intramuscular
ITV	Intravitreal
IV	Intravenous
mAb	Monoclonal antibody
PASI	Psoriasis area severity index
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD-1	Programmed cell death 1
QSS	Quasi-steady-state
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
SA	Spondylarthropathies
SC	Subcutaneous
T $\frac{1}{2}$ - β	Elimination half-life
TDM	Therapeutic drug monitoring
TMDD	Target-mediated drug disposition
TNF- α	Tumor necrosis factor alpha
UC	Ulcerative colitis
VEGF	Vascular endothelial growth factor

1 Introduction

For the last three decades, monoclonal antibodies (mAbs) have deeply improved the treatment of several diseases, including neoplasms and chronic inflammatory diseases. Their indications have been progressively extended, notably towards organ transplantation, hematology and metabolic disorders.

Therapeutic mAbs are human immunoglobulins of isotype G (IgG), which are large molecular weight (~150 kDa) hydrophilic proteins, made of two identical associations of heavy and light chain which both include constant and variable domains. The IgG present two identical antigen-binding (Fab) and one crystallizable (Fc) portion. At the extremity of the variable domain, the Fab portion has hypervariable region which binds to the specific target antigen with high affinity and specificity. The Fc portion is involved in (i) recruiting the effector systems complement component C1q, effector cells expressing FcγR at their surface, and (ii) protecting the IgG from intracellular catabolism and therefore conferring a long elimination half-life.

The first mAbs were administered intravenously (IV) but an increasing number are being administered subcutaneously (SC). The absorption following SC injection can usually be described using a slow first-order kinetic term, time of peak concentration (Tmax) being reached dafter several days.^[1-5] The pharmacokinetics of mAbs is usually described using 2-compartment models with first-order transfer rates.^[6] Central and steady-state volumes of distribution of mAbs are usually 3-5 L and 5-15 L^[1, 2, 4], respectively, values which suggest that mAbs are confined to lymphatic and blood vessels, and exhibit low (but not inexistent) tissue penetration. The elimination of IgG involves two different pathways.

- intracellular nonspecific catabolism. After cellular uptake, the Fc portion of IgGs binds to the neonatal Fc Receptor (FcRn) at acidic pH (<6.5) and thereby are protected from lysosomal degradation. IgG are addressed to the apical membrane and, when pH returns to neutral (7.4), they are released from FcRn into blood circulation. This recycling mechanism of IgG explains their long elimination half-life of approximately 3 weeks. This mechanism is saturable for IgG concentrations higher than physiologic levels.
- target-mediated specific elimination. A given mAb binds to its antigenic target with high affinity and specificity, which leads to the formation of a mAb-target complex that is eliminated by the immune system. The elimination rate of this complex, which corresponds to target-mediated elimination term of mAbs, is generally different from those of free mAb and antigenic targets.

Patients present a large variability of response with most of mAbs partly because of their large interindividual pharmacokinetic variability. This pharmacokinetic variability has been described and quantified using pharmacokinetic modelling in more than 150 studies and has been reviewed several times for the last two decades.^[1-5, 7-13]

The pharmacokinetic variability of mAbs may be explained by several individual factors. The most frequent are:

- An increase in volume of distribution and clearance with body size, as measured by body weight, height or fat-free mass);

Higher volume of distribution and clearance in male than in female;

- An increase in clearance when serum albumin decreases;
- A dramatical increase in mAb clearance when anti-drug antibodies are present, leading to low mAb concentrations and hence loss of response.

The association of these factors with pharmacokinetic parameters is generally tested and quantified using population pharmacokinetic modelling, where factors of variability are tested as covariate effect on pharmacokinetic parameters.^[14-16] A covariate which significantly increases volume of distribution and/or clearance leads to decreased mAb concentrations and vice-versa.

In addition to these factors, early works reported a decrease in elimination half-life of mAbs with either their dose (e.g. for infliximab, an anti-TNF mAb^[17, 18]), or the amount of target antigen (e.g. for rituximab, and anti-CD20 mAb)^[19]. Later, several studies reported an influence of the amount of antigenic targets on mAb pharmacokinetics. In this review, we refer to the term “antigenic mass” as being the number of antigenic target sites that are available for mAb binding. Usually, high antigenic mass was shown to be associated with low antibody concentrations, which was mainly due to high antibody elimination. The description of antigen-mediated mAb pharmacokinetics was done using target-mediated drug disposition (TMDD) models. Several reviews or methodology papers considered antigenic burden as a major factor of mAb pharmacokinetic variability that should be soundly described.^[20-26] Even if this influence was reported in several papers^[2-5, 9, 11, 27], it has never been soundly and specifically reviewed.

The aim of the present review is therefore to give an overview of the influence of antigenic mass on the pharmacokinetics of therapeutic antibodies quantified by pharmacokinetic compartmental modelling in humans.

2 Methods and literature search strategy

We focused on therapeutic antibody pharmacokinetic results obtained in humans using pharmacokinetic compartmental modelling. Indeed, compartmental modelling allows the description of absorption, distribution and elimination and has provided pharmacokinetic parameter estimates that are comparable between studies. In addition, the population approach is increasingly used, notably for mAbs.^[5] It allows the quantification of interindividual distribution of pharmacokinetic parameters by taking into account data from all individuals simultaneously. This quantification allows estimation of (i) the “mean” (referred as “typical”), (ii) the interindividual variability (referred to the “interindividual variance”) and inter-occasion variability (sometimes called the “intraindividual” variability), and (iii) the influence of individual sources of variability (referred as “covariates”) for each pharmacokinetic parameter.^[14, 15] Being based on strict quality requirements, this approach allows consistent “between-studies” comparisons.

The following query was used to search Pubmed for studies dealing with therapeutic antibody (not necessary monoclonal) pharmacokinetics using pharmacokinetic modelling (not necessary with population approach). This query has been part of our daily bibliographic follow-up:

```
(
    pharmacokinetics[Title/Abstract]
  OR pharmacokinetic[Title/Abstract]
  OR "volume of distribution"[Title/Abstract]
  OR volume[Title/Abstract]
  OR clairance[Title/Abstract]
  OR clearance[Title/Abstract]
  OR "distribution volume"[Title/Abstract]
) AND (
    monoclonal antibody[Title/Abstract]
  OR therapeutic antibody[Title/Abstract]
  OR antigen burden[Title/Abstract]
  OR antigen mass[Title/Abstract]
  OR antigenic burden[Title/Abstract]
  OR antigenic mass[Title/Abstract]
  OR tumour burden[Title/Abstract]
  OR tumour mass[Title/Abstract]
  OR tumor burden[Title/Abstract]
  OR tumor mass[Title/Abstract]
)
```

Nevertheless, this review, is not meant to be exhaustive. Publications were selected by relevance and additional articles were obtained either from their reference lists or based on our literature continuous review. On 2018-03-02, this query led to 5788 references on PubMed. Among them, 158 were pharmacokinetic modelling studies of therapeutic antibodies, published between 1996 and 2018. Of note, one study made by our group including a population pharmacokinetic study of basiliximab could not be obtained using our query. Therefore, this query may have missed other mAb pharmacokinetic modelling studies.

Among the 159 mAb pharmacokinetic modelling publications identified in the literature, 85 reported an influence of antigen mass on mAb pharmacokinetics (table 1, supplemental table).

These studies described the pharmacokinetics of 92 therapeutic antibodies, including 84 chimeric/humanized/human mAbs. The pharmacokinetics of 67 mAbs was described in only one publication, whereas for other mAbs, it was reported in more than one publication. For instance, the pharmacokinetics of adalimumab, bevacizumab, rituximab and infliximab was described in 8, 8, 9 and 14 publications, respectively. Structural pharmacokinetic models included one, two and three compartments in 31, 124 and 1 publications, respectively. Covariates (including antigenic mass) were assessed in 118 out of 159 publications.

3 Joint modelling of antibody and antigen target kinetics

3.1 Elimination of mAbs mediated by antigen targets

In pharmacokinetic models, the elimination of mAbs is usually described by both linear (non-specific) and nonlinear (specific) elimination components. The presence of target-mediated elimination has to be suspected if (i) dose-normalized concentration curves are not superposable, (ii) alterations of pharmacokinetic parameters with dose, especially an increase in clearance with decreasing doses and (iii) nonlinear elimination shape of terminal decrease of the logarithm of concentrations with time.

The joint kinetics of mAbs and their targets is described using target-mediated drug disposition (TMDD) models. The target-mediated elimination of mAbs depends on several phenomena, including the turnover of targets, the reversible binding of mAbs to their targets, and the mAb-target complex elimination. For several mAbs, TMDD modelling showed that the increase of antigen mass was associated with an increase of target-mediated elimination and therefore a decrease of their elimination half-life. The increase in target-mediated elimination is due to a much faster mAb-target complex clearance than free mAb clearance.^[28]

3.2 The TMDD system

TMDD system was introduced in 1994 by Levy^[29], investigated for an anti-D IgG in 1996 by Chapman et al.^[30] and written in its current form in 2001 by Mager et al.^[31] (figure 1A). The TMDD system is:

$$dC_1/dt = In(t) - k_{10} \cdot C_1 - k_{12} \cdot C_1 + k_{21} \cdot \frac{A_2}{V} - k_{on} \cdot R \cdot C + k_{off} \cdot RC \quad C_1(0) = 0$$

$$dA_2/dt = k_{12} \cdot C_1 \cdot V - k_{21} \cdot A_2 \quad C_2(0) = 0$$

$$dR/dt = k_{syn} - k_{deg} \cdot R - k_{on} \cdot R \cdot C + k_{off} \cdot RC \quad R(0) = k_{syn}/k_{deg}$$

$$dRC/dt = k_{on} \cdot R \cdot C - k_{off} \cdot RC - k_{int} \cdot RC \quad RC(0) = 0$$

where C_1 and A_2 are mAb concentrations in central and mAb amounts in peripheral compartments, respectively, V is central volume of distribution, R and RC are concentrations free antigen target and mAb-target complexes, respectively, $In(t)$ is antibody input function, k_{10} , k_{12} and k_{21} are first-order elimination and transfer rate constants, respectively, k_{syn} and k_{deg} are endogenous zero-order production and first-order destruction rate constants, respectively, k_{on} and k_{off} are second-order and first order association and dissociation rate constants of mAb, its target and the complex, respectively, and k_{int} is first-order complex destruction rate constant. All parameters of the TMDD system are rarely identifiable simultaneously, and approximations of this model are often made.^[20, 21, 24, 25] A comprehensive review of the different TMDD approximations has been recently released.^[32]

The concentration decay described by a TMDD model usually displays four phases^[26] (figure 2), which are, (i) rapid second-order decay due to the association of antibody to target, (ii) slow first-order decay related to unbound mAb elimination and saturated target, (iii) a mixed-order re-increase of elimination rate due to unsaturated targets and (iv) terminal decay driven by k_{off} and k_{int} . It is important to note that elimination half-life ($T_{1/2-\beta}$) is observed in phase (ii), but not in phase (iv), which slope depends not only on the β elimination phase, but also on k_{on} and k_{int} rate constants.

The absence of nonlinear shape of elimination may be due to (Figure 2D):

- antibody in stoichiometric excess compared to antigen mass, only phases (i) and (ii) are observable;
- antibody in stoichiometric default compared to antigen mass; only phases (i) and (iv) are observable.

To be *a priori* identifiable, the TMDD system necessitates measurements of C_1 , R and RC . Of note, RC amounts can be obtained indirectly, from free (R) and total (R_T) target amount measurements. In addition, the association of mAb to its target is in general much faster than the elimination of free and bound mAb and targets, k_{on} and k_{off} rate constants are identifiable *a posteriori* if sampling frequency is high, especially during the first 24 hours after mAb injection. To our knowledge, sufficiently rich measurements of the three compartments was done only for anti-CD4 (non-approved) mAbs, i.e. TRX1^[33] and MTRX1011A^[34], which led to the only two studies where all TMDD parameters (including k_{on} , k_{off} , k_{syn} , k_{deg} and k_{int}) could be estimated.

3.3 Approximations of TMDD model

3.3.1 Quasi-steady-state (QSS) approximation

If measurements of the three species are available, but sampling density is poor during the first 24 hours after infusion, the association and dissociation of mAb and target, and the dissociation and elimination of mAb-target complexes are at equilibrium, therefore only combination of k_{on} , k_{off} and k_{int} can be identified. This combination is the quasi-steady-state rate constant, i.e. $K_{SS} = (k_{off} + k_{int})/k_{on}$ (figure 1B). The QSS approximation was used to describe target-mediated kinetics of omalizumab^[35-37] (anti-IgE mAb) and of evolocumab^[38] (anti-PCSK9).

3.3.2 Approximations of TMDD models

Full or QSS TMDD model parameters cannot be identified *a priori* if measurements are available in less than C_1 , R and RC species. In studies where free (C) or total (C_T) mAb concentrations and R or R_T were available, three approximations were made:

- data transformation or model parameterization that avoid the estimation of k_{syn} , as made for etrolizumab^[39] (anti-integrins), domagrozumab^[40] (anti-mysostatin) and denosumab^[41] (anti-RANKL);
- total target amount assumed to be constant. This necessitates, to set $k_{deg} = k_{int}$, as made for canakinumab^[42-45] (anti-IL-1 β), bevacizumab^[46] (anti-VEGF) and volociximab^[47] (anti-integrins);
- binding of mAb to its target assumed irreversible (figure 1C), i.e. $k_{off} = 0$, as made for efalizumab^[48, 49] (an anti-CD11a mAb which was removed from the market in 2009) and ofatumumab^[50] (anti-CD20).

In most mAb pharmacokinetic studies, no target amounts (neither R nor R_T) are available. Three other approximations of TMDD models were made:

- a combination of constant target amount and irreversible binding assumptions, as for elotuzumab^[51] (anti-CD319), rituximab^[52] (anti-CD20) and alirocumab^[53] (anti-PCSK9);
- a combination of rapid binding and constant target amount assumptions (Wagner's approximation^[25], as made for abciximab^[54] (anti-GPIIb/IIIa);
- Michaelis-Menten approximation (see section 3.3.3).

3.3.3 Michaelis-Menten model

The Michaelis-Menten model is an approximation of TMDD based on the assumption that RT and RC amounts are constant.^[55] Under these strong conditions, the central pharmacokinetic compartment of “full” Michaelis-Menten target-mediated elimination model is defined by the following differential equation:

$$dC_1/dt = In(t) - k_{10} \cdot C_1 - k_{12} \cdot C_1 + k_{21} \cdot \frac{A_2}{V} - \frac{V_M \cdot C}{K_M + C} \quad C_1(0) = 0$$

where V_M is the maximum mAb elimination rate constant and K_M is Michaelis constant (i.e. mAb concentration corresponding to an elimination rate equal V_M/2). The parameter V_M is defined as V_M = R_T · k_{int}, whereas K_M corresponds to K_{SS}. Since Michaelis-Menten elimination does not depend on R_T, no antigen target data are necessary, but the association between antigen mass and mAb elimination cannot be quantified (figure 1D). This approximation is frequently made to describe the pharmacokinetics of mAbs in case of nonlinear shape of terminal elimination and has been used for 23 therapeutic antibodies in 28 studies (table 1). In the 18 studies where “full” Michaelis-Menten model is used^[56-72], V_M and K_M values are highly variable between studies, V_M and K_M ranges being 0.008–26.4 mg/day and 0.02–33.9 mg/L, respectively.

However, the Michaelis-Menten term has been used in simplified forms. In five studies on clenoliximab^[73] (anti CD4), alemtuzumab^[74] (anti CD52), cetuximab^[27] (anti-EGFR) otilixizumab^[75] (anti-CD3) and anti-PCSK9 mAbs (alirocumab and evolocumab)^[76], no linear (endogenous) elimination term was integrated in the model. The absence of first-order elimination term lead to apparent V_M and K_M values that may be superior than “actual” values. In studies where K_M was not identifiable, either K_M value was fixed to low values, as done for brodalumab^[77] (anti-IL-17R) and dupilumab^[78] (IL-4Rα), with values of 0.02 and 0.01 mg/L, respectively, or the Michaelis-Menten term was replaced by a zero-order elimination rate constant, as done for cetuximab^[79, 80] and basiliximab^[81] (anti-CD25). However, Michaelis-Menten models allow a quantification of the relationship between antigen mass and pharmacokinetic parameters only if antigen mass is added as a covariate on Michaelis-Menten term parameters.

3.3.4 Dose and time varying pharmacokinetic parameters

In some studies, the non-linear dose-concentration relationship, especially observed for low doses was described as an influence of dose on volume of distribution^[82-85] or as a time-varying

volume.^[86] The increase in volume for low doses and/or low mAb concentrations was consistent with a capture of mAbs by antigen targets. Besides, some studies described an antibody clearance decreasing with time. This description is in accordance with a target-mediated clearance and with antigen mass being maximal at the beginning of treatment and decreasing with time.^[87-90] However, these models do not allow either a mechanistic description or quantification of the effect of antigen mass.

3.3.5 Antigen mass as a covariate on target-mediated elimination parameters

The absence of target measurements prevent actual target amount parameters (such as R_0 , k_{syn} , k_{out} , R_T or k_{int}) from being estimated. For instance, in Michaelis-Menten models, V_M depends on both R_T and k_{int} , which are not separable. In time-varying models, no information about antigen amount can be obtained from the exponential decrease of clearance.^[87-90] As a consequence, these models cannot be used in mAb pharmacokinetics simulations for different target amount values. To overcome this drawback, antigen mass measurements can be added as covariates on pharmacokinetic parameters (figure 1E): for instance, target-mediated clearance of rituximab was found to increase with circulating CD20 target.^[52]

Indirect antigen burden measurements, such as tumor size, were used as covariates,. For pembrolizumab (anti-PD-1), increased tumour size was associated with maximum time-varying clearance value of pembrolizumab (anti-PD1), whereas better clinical response was associated with decreased time to reach minimum clearance.^[89] Tumor size was associated with altered clearance decrease rate of obinutuzumab (anti-CD20).^[91]

4 Target-mediated elimination and apparent linear pharmacokinetics

Theoretically, the influence of antigen mass on pharmacokinetics and TMDD models apply to all antibodies. Indeed, some mAbs, such as cetuximab^[27, 79, 80], efalizumab^[48, 49, 71, 92] and omalizumab^[35-37] displayed nonlinearity in all publications. Trastuzumab showed either presence^[69, 93] or absence^[94, 95] of nonlinear elimination. Rituximab showed nonlinear pharmacokinetics for chronic lymphocytic leukemia (CLL)^[52, 90] but not for other B-cell malignancies^[96-98] or RA.^[99, 100] For some of them, as anti-TNF mAbs, nonlinearity was never observed in 26 publications, with infliximab^[101-114], adalimumab^[115-122], certolizumab pegol^[123, 124] and golimumab.^[125-128] This may be due to an excess of anti-TNF mAbs compared to TNF- α concentrations.^[4] Out of the 85 pharmacokinetic publications that reported an influence of antigen mass, 35 used linear pharmacokinetic models (table 1); an increased mAb clearance with higher antigen mass levels may be due to a higher antigen turnover (i.e. higher k_{syn} and/or lower k_{deg} values).

It can reasonably be hypothesized that chimeric, humanized and human antibodies, which present human Fc portion, should present an elimination half life ($T_{1/2-\beta}$) similar to endogenous IgGs in humans (21 days [129]). However, for some mAbs, dramatic differences in values of pharmacokinetic parameters were reported between publications. However, it should be kept in mind that $T_{1/2-\beta}$ is only apparent and may depend on antigen mass and its interactions with mAbs (R_T , k_{on} and k_{int}): decreased R_T , but increased k_{on} and k_{int} are all associated with increased terminal half-life. Terminal half-life will be noted $T_{1/2R}$ to keep in mind the participation of antigen mass on apparent elimination half-life.

4.1 Antigen mass as a covariate of pharmacokinetic parameters

In studies where no apparent nonlinear decay was observed, target-mediated elimination parameters could not be identified. The influence of target on mAb elimination was described by inclusion of a covariate associated with elimination rate constant, clearance and/or volume of distribution (figure 3). Covariates may reflect target turnover, as described using R_T , k_{syn} or k_{deg} . Among the 85 publications which reported an influence of antigen mass, 29 reported an influence of a covariate related to antigen mass on pharmacokinetic parameters (table 1). Among these, pre-therapeutic measurements of circulating antigenic targets were found to be associated with pharmacokinetic parameters in 5 publications:

- VEGF-A concentration for bevacizumab^[130];
- extracellular domain of HER2 for trastuzumab^[95] and trastuzumab emtansine^[131];
- complement component 5 (C5) for eculizumab^[132];
- CD19+ (B-cell) counts for rituximab.^[99]

Concentrations of circulating antigenic targets, when available, show consistently an influence of antigen burden on mAb pharmacokinetics. However, circulating targets may not be fully sensitive, i.e. may be an underestimation of total antigen mass, especially if part of antigenic target amount is not circulating.

4.2 Indirect antigen mass measurement using covariates

Beside direct target antigen level measurements, some covariates provide an indirect quantification of antigen mass, as tumor size for anti-cancer mAbs, disease activity and pharmacodynamic biomarker levels (see section 5.2).

4.2.1 Influence of tumor size

Tumor size is a relevant measurement of antigen mass if it is related to the amount of antigenic targets, but it may be less specific, because it is influenced by components other than antigen mass (Figure 1E). Since techniques of tumor size measurements and their target-antigen density are very different between type of cancer, it is difficult to deliver a global message on the influence of tumor size on mAb pharmacokinetics, even if 7 publications reported and increase in mAb clearance with pre-therapeutic tumour size (table 1):

- breast cancer size for trastuzumab^[94] and trastuzumab emtansine^[131, 133];
- bladder urothelial carcinoma size for atezolizumab^[134];
- size of various solid tumors for olaratumumab^[135] and pembrolizumab^[136];
- and the number of extrahepatic metastases for bevacizumab^[130].

4.2.2 Influence of disease activity

Similarly to tumor size, disease activity may be a relevant marker of antigen mass, but it may be less specific than tumor size and, in addition, its measurement is more subjective. The influence of disease activity on mAb pharmacokinetics is inconstant. Five publications reported an increase in mAb clearance with disease activity scores (figure 3, table 1):

- Eastern Cooperative Oncology Group (ECOG) is an integer numeral score between 0 (asymptomatic) and 5 (death) in cancer patients that was associated with clearance of pembrolizumab^[136] and tremelimumab^[137];
- Psoriasis Area Severity Index (PASI) is a decimal number between 0 (asymptomatic) and 72 (maximal) that was associated with clearance of efalizumab^[92] and guselkumab^[138] (anti-IL-23);
- Harwey-Bradshaw index (HBI) in Crohn's disease patients is an integer number between 0 (asymptomatic) and 26 (maximal) that was associated with clearance of infliximab.^[103]

4.2.3 Influence of biomarkers

Measurement of concentrations of a biomarker related to antigen mass are often preferred to disease activity scores because it has a higher objectivity, but, similarly to tumor size and disease activity scores, it may be less specific of antigen mass and inconstantly found to be related to mAb pharmacokinetics. Eight publications reported an increase in mAb clearance with pre-therapeutic levels of a biomarker (Figure 3, table 1):

- Lymphocyte counts for efalizumab^[92], even if the link between CD11a expression and total lymphocyte count may be considered as very indirect;
- Carcino-embryonic antigen (CEA) concentration for bevacizumab^[130] is indirectly related to tumour burden but not with VEGF concentrations (see section 5.2);

- Concentration of C-reactive protein (CRP) for anti-TNF biopharmaceuticals. In early studies, pre-therapeutic CRP levels were found to be inversely related with steady-state concentrations of infliximab concentrations.^[139, 140] The pharmacokinetics of anti-TNF mAbs (infliximab, adalimumab, certolizumab pegol, golimumab) was described in 28 publications, using one or 2-compartment models with first-order transfer and elimination rate constants (table 2). Nonlinear elimination was reported in none of these publications. The association of CRP with anti-TNF mAb pharmacokinetic parameters was assessed in 16 publications, mainly using a power transformation, i.e. $\theta_{TV} = \theta_{pop} \cdot [CRP / med(CRP)]^\beta$, where θ_{TV} and θ_{pop} are typical and population estimates of pharmacokinetic parameters, CRP are serum levels of CRP (usually given in mg/L), med(CRP) is median value of CRP and β is an allometric parameter quantifying the effect of CRP on θ . Significant association between CRP levels and mAb clearance was found in 7 publications out of 16: for adalimumab (in 1 study in hydradenitis suppurativa), infliximab (in 2 publications in rheumatoid arthritis and Crohn's disease), golimumab (in 2 publications in spondylarthropathies) and certolizumab pegol (in 2 publications that used the same inflammatory bowel disease population). Except for one study of certolizumab pegol where CRP was assessed as categorical, estimated values of β ranged from 0.05 to 0.17. The influence of CRP levels on mAb clearance may be explained by target-mediated drug disposition. Because an increase in TNF- α leads to an increase in CRP concentrations, CRP may indeed be considered as an indirect marker of antigenic target concentrations.^[141-143] Increased clearance in presence of high CRP levels may be explained by increased levels of targets, and therefore increased target-mediated elimination.

4.2.4 Influence of disease

In some studies, pharmacokinetic models were developed using pooled data from several trials and thus are susceptible to include several diseases or subtypes of diseases. In 7 publications, the type or subtype of disease was associated with differences in pharmacokinetic parameters.^[67, 70, 107, 136, 144-146] One of possible reasons of such differences are differences in amount and turnover (R_T , k_{syn} , k_{deg} , see section 4.2), and localization (and therefore the accessibility by mAb) of antigenic targets. The 4 studies of anticancer mAbs that reported different mAb clearances among types of tumour did not investigate pathophysiological reasons of such differences. Besides, in inflammatory bowel diseases (IBD), 2 publications reported volumes of distribution and clearances of infliximab^[107] and of vedolizumab^[70] slightly superior for ulcerative colitis than for Crohn's disease, but again, there is no evidence of differences in antigen mass due to diseases. However, the intrinsic catabolism rate of a given mAb might be modified between diseases. Notably, FcRn expression was suggested to be increased with inflammation, which would lead to an decrease in mAb intrinsic clearance.^[4]

Elimination half-life ($T_{1/2R}$) estimates of bevacizumab was 21 days in teleangiectasia^[147], 17-20 days in various solid tumours^[148, 149], 15-17 days in child sarcoma^[144, 150], and 19 days in colorectal cancer (CRC) and, surprisingly, 44 days in multi-metastatic CRC.^[130] For trastuzumab, $T_{1/2R}$ was 28 days in metastatic breast cancer (BC), but highly controversial in early BC, 12 days^[94] or 40 days.^[69] The pharmacokinetics of rituximab is highly variable between diseases: $T_{1/2R}$ is approximately 20 days in follicular non-Hodgkin lymphoma^[97] and in RA^[49, 99] and 40-100 days in diffuse large B cell lymphoma (DLBCL).^{[96, 98, 151].}

However, a strong limitation of inter-study comparison of pharmacokinetic parameter values is made by differences in techniques of mAb concentration measurements. Indeed, different techniques may lead to differences in concentration values and in estimates of pharmacokinetic parameters.^[152] In this context, infliximab concentrations were measured in a cohort of patients with various diseases using a single ELISA technique in the same lab.^[112] This study confirmed that infliximab $T_{1/2R}$ was 14-15 days, except in RA (10 days) and showed that infliximab clearance in rheumatoid arthritis (RA) was almost twice that estimated in spondylarthropathies (SA). This may be explained by TMDD, because TNF- α burden is higher in RA than in AS^[153], with high TNF- α burden in blood^[154] and synovial fluids^[155] of RA patients. In IBD, a high infliximab clearance was found similarly to RA again an observation which may be explained by TMDD. The hypothesis of TMDD here is consistent with the reported increase in infliximab clearance with CRP levels in RA^[111] and IBD.^[110]

4.2.5 Influence of concomitant treatment

Drug interactions with mAbs were reviewed elsewhere^[156] and this part deals with drug interactions related to antigen mass (figure 3). The concentrations of anti-TNF biopharmaceuticals (infliximab, adalimumab) were shown to increase when methotrexate, an inhibitor of dihydrofolate reductase, is co-administered notably in RA patients^[157]. Pharmacokinetic modelling studies of infliximab showed that immunomodulator (such as methotrexate) co-treatment is associated with lower infliximab clearance^[105, 111], independently from CRP levels.^[111] Our hypothesis was that methotrexate anti-inflammatory activity may contribute to a substantial decrease in TNF- α levels, thereby leading to a decreased target-mediated clearance of infliximab. This mechanism appears to be independent to the immunosuppressant activity of methotrexate, involved in the prevention of anti-drug antibody development.^[158] The proof of this mechanism will be obtained by the description of target-mediated drug disposition of anti-TNF biodrugs. This will necessitate measurements of both levels of total TNF- α and TNF- α unbound to mAb. To date, no sound evidence is available to show that drugs other than methotrexate decrease TNF- α levels.

The modulation of target amount by cotreatment was more thoroughly investigated for anti-PCSK9 mAbs, for which clearance was shown to be higher in patients co-treated with statins.^[38, 53, 76, 156] An evolocumab study using a TMDD model showed that PCSK9 levels were higher in patients treated with statins.^[38] This increase in PCSK9 levels may lead to higher target-mediated clearance of anti-PCSK9 mAbs.

However, the influence of comedication on mAb pharmacokinetics may be due to other (unknown) factors. Differences in cetuximab clearance that were reported between protocols of chemotherapies,^[80] and the increase in clearance of guselkumab in presence of anti-inflammatory drugs are still unexplained.^[138]

4.2.6 Influence of *FCGR3A* genotype

The gene *FCGR3A* encodes the low affinity receptor of the Fc portion of IgG, Fc γ RIIIA, which is expressed at the surface of effector cells, as natural killer (NK) cells. This receptor presents a single nucleotide polymorphism, the *FCGR3A*-158 V/F polymorphism, which generates two

allotypes of FcγRIIIA, with either a valine (V) or a phenylalanine (F) at position 158. *In vitro*, human IgG present a higher affinity for allele V than for allele F. *In vivo*, a better clinical response of follicular non-Hodgkin patients treated with rituximab was observed in homozygous V/V than in F carriers.^[159, 160] This better clinical response of V/V patients was reported for other cytotoxic antibodies, cetuximab in colorectal cancer^[161] and trastuzumab in breast cancer.^[162] This genotype was shown to influence the concentration-effect relationship of anti-thymocyte globulins (ATG) in renal transplant patients: V/V patients had a higher sensitivity to treatment than F carriers.^[86, 163] All these cytotoxic antibodies have in common action, at least in part, by antibody dependent cellular cytotoxicity (ADCC): the Fc portion of mAb binds to FcγRIIIA, which leads to the lysis of target cell by the effector cell. In IBD patients, infliximab was shown to induce ADCC of inflammatory cells^[164, 165] and V/V patients were shown to have a better biological response than F carriers.^[166, 167] In IBD patients treated by infliximab who were in remission and in whom infliximab treatment was stopped, V/V genotype was associated with an increased infliximab clearance and, for those with a CRP > 5 mg/L, with a shorter time to relapse. Taken together, these results are in accordance with a better efficacy, but a higher “consumption” of infliximab in V/V patients, leading to underexposure to infliximab. The link between *FCGR3A*-158 V/F polymorphism, antigen mass and mAb consumption was finally established in CLL patients treated with rituximab: target-mediated elimination of rituximab increased with increased CD20+ cell count and was in V/V patients, rituximab endogenous clearance remaining unchanged (Figures 1F and 3). These findings suggest that increased affinity of V allele for Fc portion leads to increased mAb-cell complex formation and elimination by ADCC, and therefore increased mAb target-mediated drug disposition of mAbs acting at least partly by ADCC, such as rituximab, infliximab and others.

5 Beyond target-mediated clearance

5.1 Retention of mAb by antigenic targets

In addition to mAb clearance, a few studies have described an association between antigen mass and volume of distribution. The influence of antigen mass on mAb disposition may be explained by its irreversible (target-mediated “elimination”) or reversible (target-mediated “retention”) interactions of mAbs. Increased target-mediated elimination or retention lead to decreased and increased $T_{1/2R}$, respectively, and both lead to decreased mAb concentrations. Increased extracellular domain of HER2 (HER2-ECD) was associated with increasing trastuzumab central volume of distribution^[95], with a modest influence on $T_{1/2R}$, which ranged from 26 to 39 days for HER2-ECD concentrations ranging from 1.7 to 2431 ng/mL.

Retention of rituximab was marked in DLBCL patients. Increased tumor volume was associated with increasing rituximab central and peripheral volumes of distribution, resulting in $T_{1/2R}$ values ranging from 13 to 84 days, for tumor volumes ranging from 17 to 4339 cm³.^[98] The retention of rituximab may explain, at least in part, the differences in values of pharmacokinetic parameters between follicular lymphoma and RA on one hand, and DLBCL in the other hand. Of note, the type of disease was associated with volume variations of:

- ganitumab^[146], volume of distribution being higher in pancreatic cancer patients than others;
- infliximab^[107], volume of distribution being increased by 25% in IBD compared than in other diseases (spondylarthropathies, RA). Apparent increase in volume of distribution in IBD is associated with an increase in $T_{1/2R}$. This may therefore be due to lower R_T , higher k_{out} and/or k_{int} values in IBD compared to RA or spondylarthropathies (figure 2D). This might be explained by pathophysiological particularities of IBD, for which part of antigen mass may lead to altered infliximab affinity and/or complex elimination. However, this hypothesis was never mechanistically investigated.

5.2 Antigenic targets present in several tissues

The TMDD model described in section 4 assumes a zero-order input and a homogeneous one-compartment distribution of antigenic targets. These assumptions are often made for practical considerations, but may not hold in some cases. Indeed, for instance, antigenic targets may be both circulating and cellular. Increased clearance of trastuzumab and trastuzumab emtansin was associated with pre-therapeutic tumour burden^[94, 131, 133] and HER2-ECD^[95, 131], which may represent cellular and circulating HER2, respectively. Increased bevacizumab clearance was associated with pre-therapeutic VEGF and ACE serum concentrations, and the number of extrahepatic metastases.^[130] The circulating VEGF is only a part of total VEGF available for bevacizumab binding. Being higher inside the tumor and in the microenvironment^[168], total VEGF burden should increase with tumour size and number of metastases. Thus, circulating and non-circulating (cellular) antigen mass both provide information on total target antigen amount (figure 3). The pharmacokinetics of antibodies which bind to both membrane and soluble antigens may be described using TMDD models for drugs that bind to more than one target^[169], but which, to our knowledge, was done only in animals. Indeed, in cynomolgus monkeys, the pharmacokinetics of MNRP1685A an anti-neuropilin-1 (NRP1) mAb, was described using a

simplified TMDD model with drug binding to both membrane and circulating antigen targets and was shown to be less influenced by circulating than membrane antigen mass.^[170]

6 Conclusions

Among factors of variability of the pharmacokinetics of therapeutic antibodies, antigen mass has been one of the most frequently reported, in more than half of pharmacokinetic modelling studies. Antigen mass influence may result in different pharmacokinetic profiles for different antibodies in different diseases, and was described using a number of modelling strategies. Because, theoretically, all chimeric, humanized and human monoclonal antibodies are similar to endogenous IgG, important differences are observed between antibodies and diseases, which are due, at least in part, to target antigen mass. Structural pharmacokinetic model describing antibodies is bicompartimental[6, 171], and target-mediated drug disposition (TMDD) models are used to describe antibody and target joint kinetics.

Since the presence of mAb nonlinear elimination is associated with non-saturation of antigen mass, and therefore with an increased risk of inefficacy or relapse (see section 3), dosing regimens should be defined to avoid nonlinear elimination as much as possible. Thus, the influence of antigen mass has to be soundly explored starting from early clinical phases. Notably, dose-ranging studies in humans should provide a sound inspection of pharmacokinetic profiles. An influence of antigen mass is likely to be significant in case of (i) nonlinear elimination shapes, (ii) increase in mAb clearance for decreasing doses (by unit of body size) and (iii) absence of superposition of dose-normalized concentration-curves and AUC. In addition, a sound description of TMDD pharmacokinetics is necessary to evaluate the weight of antigen mass on total pharmacokinetic variability. This description is based on:

- Antibody concentration measurements which should reflect the concentration of antibody unbound to target. This is usually done by ELISA and/or HPLC-MS/MS techniques[172];
- Measurements of antigenic target unbound to mAb and, if possible, measurement of complexes or total target amounts.
- Dense sampling strategies for both antibody and target amounts to ensure accurate estimates of TMDD model parameters, especially during the early phase, which is necessary to identify association (k_{on}) and dissociation (k_{off}) rates of mAb and targets, in addition to parameters of exchanges between central and peripheral compartments.^[173]

The influence of antigen mass should be accounted for the determination of first-in-human dose^[174, 175], notably because it cannot be derived from drug-free kinetics or from animal data. For instance, the pharmacokinetics of rituximab in xenografted mice is very different from that in humans with either non-Hodgkin lymphoma^[96-98, 151] or LLC.^[52, 90] Since the turnover of target burden is very different between diseases, and between patients and animal models, procedures determining the first-in-man dose may benefit from prediction strategies of target-mediated drug disposition for mAbs. These predictions are achieved with the determination of TMDD parameters.^[22]

For some mAbs, TMDD models were used to estimate the dose needed to saturate mAb target-mediated elimination in most of patients, as for evolocumab^[38] or obinutuzumab.^[91] This approach may however lead to over-exposure of patients with low target antigen levels. TMDD models may be used to estimate the dose and/or schedule necessary to saturate target antigen in each patient individually. For instance, eculizumab concentration leading to a good clinical response^[132] (with a total saturation and inactivation of C5 component of complement) and concentration associated with departure from linearity^[60] are the same (100 mg/L). A good

strategy would be to calculate eculizumab dose and/or dosing interval so that each patient has trough concentrations always > 100 mg/L.

An even better strategy would be to adjust the dose to the amount of antigens. At present, this is done only with omalizumab, which dosing schedule depends not only on body weight, but also on baseline IgE concentration. The benefit of dosing adjustment to antigen mass should depend on its participation in total pharmacokinetic variability. For instance, adjusting the dose of rituximab to CD20 count in LLC patients may not lead to a clinical benefit, because antigen mass explains less than 5% of pharmacokinetic variability^[52], whereas it should lead to an improvement of treatment of DLBCL for which tumour burden explains more than 40% of rituximab pharmacokinetic variability.^[98]

The observation of linear pharmacokinetics is often interpreted as a saturation of the target antigen by mAb. However, apparent linear pharmacokinetics does not necessarily imply an actual saturation of antigenic target by mAb, notably in the “extreme” case where antibody is in stoichiometric default compared to antigen (with only phases (i) and (iv) of the four TMDD phases^[26] figure 2). Indeed, apparent linear pharmacokinetics is often accompanied by and influence of antigen mass, as reported for anti-TNF antibodies^[110, 111, 116, 123], trastuzumab^[94, 95] and trastuzumab emtansine^[131, 133], and bevacizumab.^[130] In addition, the appearance of linear pharmacokinetics does not mean that antigenic targets are totally saturated and that dose is optimal. This is especially obvious for DLBCL patients treated by rituximab: patients with high tumour volume were clearly shown to be underexposed to rituximab and therefore would benefit from an increased dose, despite linear pharmacokinetics.^[98] In clinical practice, antibody concentrations associated with *in vivo* target saturation are not known, but they should be less relevant than concentrations predictive of good clinical response, which are approximately 3-7 mg/L for infliximab and adalimumab in chronic inflammatory diseases^[176] and 15 mg/L for bevacizumab in mCRC.^[130]

As other individual factors of variability, antigen mass is susceptible to influence not only inter-, but also intra-individual variability of mAb pharmacokinetics. In this context, disease relapse or flare may be accompanied by an increase of antigen mass, and therefore decreased concentrations. Ideally, an optimal scheme should be found for each treated patient, verified regularly and amended if necessary. Optimal treatment schemes were proposed, based on pharmacokinetic modelling, notably in the context of therapeutic drug monitoring of anti-TNF mAbs.^[176] Model-based therapeutic drug monitoring (TDM) of mAbs include individual factors of variability and mAb concentration measurements. No TDM model or procedure includes antigen mass measurements yet. Future improvements of model-based dosing optimization techniques will be likely obtained by implementation of the influence of antigen mass on the pharmacokinetics of therapeutic antibodies.

Compliance with Ethical Standards

Acknowledgements. This work was partly supported by the French Higher Education and Research Ministry under the program ‘Investissements d’avenir’ Grant Agreement: LabEx MAbImprove ANR-10-LABX-53-01.

Disclosure. David Ternant has given lectures for Amgen and Sanofi. Gilles Paintaud reports grants received by his research team, from Novartis, Roche Pharma, Sanofi-Genzyme, Chugai and Pfizer, outside of the submitted work. Theodora Bejan-Angoulvant, William Raoul and Nicolas Azzopardi have nothing to declare.

7 References

1. Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. *Clin*. 2010;49(10):633-59. doi: 10.2165/11535960-000000000-00000.
2. Dostalek M, Gardner I, Gurbaxani BM, Rose RH, Chetty M. Pharmacokinetics, pharmacodynamics and physiologically-based pharmacokinetic modelling of monoclonal antibodies. *Clin Pharmacokinet*. 2013;52(2):83-124.
3. Mould DR, Sweeney KR. The pharmacokinetics and pharmacodynamics of monoclonal antibodies--mechanistic modeling applied to drug development. *Curr Opin Drug Discov Dev*. 2007;10(1):84-96.
4. Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G. Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis. *Clin Pharmacokinet*. 2015;54(11):1107-23.
5. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 2008;84(5):548-58. doi: 10.1038/clpt.2008.170. Epub Sep 10.
6. Fronton L, Pilari S, Huisinga W. Monoclonal antibody disposition: a simplified PBPK model and its implications for the derivation and interpretation of classical compartment models. *J Pharmacokinet Pharmacodyn*. 2014;41(2):87-107.
7. Breedveld FC. Therapeutic monoclonal antibodies. *Lancet*. 2000 Feb 26;355(9205):735-40.
8. Liu L. Pharmacokinetics of monoclonal antibodies and Fc-fusion proteins. *Protein Cell*. 2018;9(1):15-32.
9. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci*. 2004;93(11):2645-68.
10. Ryman JT, Meibohm B. Pharmacokinetics of Monoclonal Antibodies. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(9):576-88.
11. Ternant D, Paintaud G. Pharmacokinetics and concentration-effect relationships of therapeutic monoclonal antibodies and fusion proteins. *Expert Opin Biol Ther*. 2005;5(Suppl 1):S37-47.
12. Yu T, Enioutina EY, Brunner HI, Vinks AA, Sherwin CM. Clinical Pharmacokinetics and Pharmacodynamics of Biologic Therapeutics for Treatment of Systemic Lupus Erythematosus. *Clin Pharmacokinet*. 2017;56(2):107-25.
13. Gill KL, Machavaram KK, Rose RH, Chetty M. Potential Sources of Inter-Subject Variability in Monoclonal Antibody Pharmacokinetics. *Clin Pharmacokinet*. 2016;55(7):789-805.
14. Duffull SB, Wright DF, Winter HR. Interpreting population pharmacokinetic-pharmacodynamic analyses - a clinical viewpoint. *Br J Clin Pharmacol*. 2011;71(6):807-14.
15. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol*. 2013;2013(17):14.
16. Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokinet Biopharm*. 1977 Oct;5(5):445-79.
17. FDA. Infliximab. Clinical pharmacology review. Accessed at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107704.pdf> (21/08/2014).

18. FDA. Infliximab label information. Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s53591bl.pdf (02/03/2018).
19. Berinstein NL, Grillo-Lopez AJ, White CA, Bence-Bruckler I, Maloney D, Czuczman M, et al. Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol*. 1998 Sep;9(9):995-1001.
20. Gibiansky L, Gibiansky E. Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic-pharmacodynamic modeling of biologics. *Expert Opin Drug Metab Toxicol*. 2009;5(7):803-12. doi: 10.1517/17425250902992901.
21. Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*. 2008;35(5):573-91. doi: 10.1007/s10928-008-9102-8. Epub 2008 Nov 13.
22. Luu KT, Bergqvist S, Chen E, Hu-Lowe D, Kraynov E. A model-based approach to predicting the human pharmacokinetics of a monoclonal antibody exhibiting target-mediated drug disposition. *J Pharmacol Exp Ther*. 2012;341(3):702-8.
23. Luu KT, Boni J. A method for optimizing dosage regimens in oncology by visualizing the safety and efficacy response surface: analysis of inotuzumab ozogamicin. *Cancer Chemother Pharmacol*. 2016;78(4):697-708.
24. Ma P. Theoretical considerations of target-mediated drug disposition models: simplifications and approximations. *Pharm Res*. 2012;29(3):866-82.
25. Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *Pharm Res*. 2005;22(10):1589-96. doi: 10.007/s11095-005-6650-0. Epub 2005 Sep 22.
26. Peletier LA, Gabrielsson J. Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification. *J Pharmacokinet Pharmacodyn*. 2012;39(5):429-51.
27. Dirks NL, Nolting A, Kovar A, Meibohm B. Population pharmacokinetics of cetuximab in patients with squamous cell carcinoma of the head and neck. *J Clin Pharmacol*. 2008;48(3):267-78. doi: 10.1177/0091270007313393. Epub 2008 Jan 24.
28. Tabrizi MA, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug Discov Today*. 2006;11(1-2):81-8.
29. Levy G. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther*. 1994;56(3):248-52.
30. Chapman GE. A pharmacokinetic/pharmacodynamic model for the action of anti-D immunoglobulin in effecting circulatory clearance of Rh D+ red cells. *Transfus Med*. 1996;6(3):227-33.
31. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn*. 2001;28(6):507-32.
32. Lixoft. Target-mediated drug disposition (TMDD) model library. Accessed at: <http://mlxtran.lixoft.com/libraries/target-mediated-drug-disposition-tmdd-model-library/> 2017.
33. Ng CM, Stefanich E, Anand BS, Fielder PJ, Vaickus L. Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. *Pharm Res*. 2006;23(1):95-103. Epub 2006 Nov 30.
34. Zheng Y, Scheerens H, Davis JC, Jr., Deng R, Fischer SK, Woods C, et al. Translational pharmacokinetics and pharmacodynamics of an FcRn-variant anti-CD4 monoclonal antibody from preclinical model to phase I study. *Clin Pharmacol Ther*. 2011;89(2):283-90.

35. Hayashi N, Tsukamoto Y, Sallas WM, Lowe PJ. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol*. 2007;63(5):548-61. Epub 2006 Nov 10.
36. Honma W, Gautier A, Paule I, Yamaguchi M, Lowe PJ. Ethnic sensitivity assessment of pharmacokinetics and pharmacodynamics of omalizumab with dosing table expansion. *Drug Metab Pharmacokinet*. 2016;31(3):173-84.
37. Lowe PJ, Tannenbaum S, Gautier A, Jimenez P. Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. *Br J Clin Pharmacol*. 2009;68(1):61-76. doi: 10.1111/j.365-2125.009.03401.x.
38. Gibbs JP, Doshi S, Kuchimanchi M, Grover A, Emery MG, Dodds MG, et al. Impact of Target-Mediated Elimination on the Dose and Regimen of Evolocumab, a Human Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). *J Clin Pharmacol*. 2017;57(5):616-26.
39. Wei X, Gibiansky L, Wang Y, Fuh F, Erickson R, O'Byrne S, et al. Pharmacokinetic and Pharmacodynamic Modeling of Serum Etrolizumab and Circulating beta7 Receptor Occupancy in Patients With Ulcerative Colitis. *J Clin Pharmacol*. 2017;2017(26).
40. Bhattacharya I, Manukyan Z, Chan P, Heatherington A, Harnisch L. Application of Quantitative Pharmacology Approaches in Bridging Pharmacokinetics and Pharmacodynamics of Domagrozumab From Adult Healthy Subjects to Pediatric Patients With Duchenne Muscular Disease. *J Clin Pharmacol*. 2017;2017(12).
41. Gibiansky L, Sutjandra L, Doshi S, Zheng J, Sohn W, Peterson MC, et al. Population pharmacokinetic analysis of denosumab in patients with bone metastases from solid tumours. *Clin*. 2012;51(4):247-60. doi: 10.2165/11598090-000000000-00000.
42. Ait-Oudhia S, Lowe PJ, Mager DE. Bridging Clinical Outcomes of Canakinumab Treatment in Patients With Rheumatoid Arthritis With a Population Model of IL-1beta Kinetics. *CPT Pharmacometrics Syst Pharmacol*. 2012;2012(26):6.
43. Chakraborty A, Tannenbaum S, Rordorf C, Lowe PJ, Floch D, Gram H, et al. Pharmacokinetic and pharmacodynamic properties of canakinumab, a human anti-interleukin-1beta monoclonal antibody. *Clin*. 2012;51(6):e1-18. doi: 10.2165/11599820-000000000-00000.
44. Chakraborty A, Van LM, Skerjanec A, Floch D, Klein UR, Krammer G, et al. Pharmacokinetic and pharmacodynamic properties of canakinumab in patients with gouty arthritis. *J Clin Pharmacol*. 2013;53(12):1240-51.
45. Sun H, Van LM, Floch D, Jiang X, Klein UR, Abrams K, et al. Pharmacokinetics and Pharmacodynamics of Canakinumab in Patients With Systemic Juvenile Idiopathic Arthritis. *J Clin Pharmacol*. 2016;56(12):1516-27.
46. Panoilia E, Schindler E, Samantas E, Aravantinos G, Kalofonos HP, Christodoulou C, et al. A pharmacokinetic binding model for bevacizumab and VEGF165 in colorectal cancer patients. *Cancer Chemother Pharmacol*. 2015;75(4):791-803.
47. Ng CM, Bai S, Takimoto CH, Tang MT, Tolcher AW. Mechanism-based receptor-binding model to describe the pharmacokinetic and pharmacodynamic of an anti-alpha5beta1 integrin monoclonal antibody (volociximab) in cancer patients. *Cancer Chemother Pharmacol*. 2010;65(2):207-17.
48. Bauer RJ, Dedrick RL, White ML, Murray MJ, Garovoy MR. Population pharmacokinetics and pharmacodynamics of the anti-CD11a antibody hu1124 in human subjects with psoriasis. *J Pharmacokinet Biopharm*. 1999;27(4):397-420.

49. Ng CM, Joshi A, Dedrick RL, Garovoy MR, Bauer RJ. Pharmacokinetic-pharmacodynamic-efficacy analysis of efalizumab in patients with moderate to severe psoriasis. *Pharm Res.* 2005 Jul;22(7):1088-100. Epub 2005 Jul 22.
50. Struemper H, Sale M, Patel BR, Ostergaard M, Osterborg A, Wierda WG, et al. Population pharmacokinetics of ofatumumab in patients with chronic lymphocytic leukemia, follicular lymphoma, and rheumatoid arthritis. *J Clin Pharmacol.* 2014;54(7):818-27.
51. Gibiansky L, Passey C, Roy A, Bello A, Gupta M. Model-based pharmacokinetic analysis of elotuzumab in patients with relapsed/refractory multiple myeloma. *J Pharmacokinet Pharmacodyn.* 2016;43(3):243-57.
52. Tout M, Gagez AL, Lepretre S, Gouilleux-Gruart V, Azzopardi N, Delmer A, et al. Influence of FCGR3A-158V/F Genotype and Baseline CD20 Antigen Count on Target-Mediated Elimination of Rituximab in Patients with Chronic Lymphocytic Leukemia: A Study of FILO Group. *Clin Pharmacokinet.* 2016;2016:25.
53. Djebli N, Martinez JM, Lohan L, Khier S, Brunet A, Hurbin F, et al. Target-Mediated Drug Disposition Population Pharmacokinetics Model of Alirocumab in Healthy Volunteers and Patients: Pooled Analysis of Randomized Phase I/II/III Studies. *Clin Pharmacokinet.* 2017;56(10):1155-71.
54. Mager DE, Mascelli MA, Kleiman NS, Fitzgerald DJ, Abernethy DR. Simultaneous modeling of abciximab plasma concentrations and ex vivo pharmacodynamics in patients undergoing coronary angioplasty. *J Pharmacol Exp Ther.* 2003 Dec;307(3):969-76. Epub 2003 Oct 08.
55. Yan X, Mager DE, Krzyzanski W. Selection between Michaelis-Menten and target-mediated drug disposition pharmacokinetic models. *J Pharmacokinet Pharmacodyn.* 2010;37(1):25-47.
56. Admiraal R, van Kesteren C, Jol-van der Zijde CM, van Tol MJ, Bartelink IH, Bredius RG, et al. Population pharmacokinetic modeling of Thymoglobulin((R)) in children receiving allogeneic-hematopoietic cell transplantation: towards improved survival through individualized dosing. *Clin Pharmacokinet.* 2015;54(4):435-46.
57. Chudasama VL, Schaedeli Stark F, Harrold JM, Tibbitts J, Girish SR, Gupta M, et al. Semi-mechanistic population pharmacokinetic model of multivalent trastuzumab emtansine in patients with metastatic breast cancer. *Clin Pharmacol Ther.* 2012;92(4):520-7.
58. Frey N, Grange S, Woodworth T. Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. *J Clin Pharmacol.* 2010;50(7):754-66.
59. Galluppi GR, Wisniacki N, Stebbins C. Population pharmacokinetic and pharmacodynamic analysis of BIIB023, an anti-TNF-like weak inducer of apoptosis (anti-TWEAK) monoclonal antibody. *Br J Clin Pharmacol.* 2016;82(1):118-28.
60. Gatault P, Brachet G, Ternant D, Degenne D, Recipon G, Barbet C, et al. Therapeutic drug monitoring of eculizumab: Rationale for an individualized dosing schedule. *MAbs.* 2015;7(6):1205-11.
61. Gupta A, Hussein Z, Hassan R, Wustner J, Maltzman JD, Wallin BA. Population pharmacokinetics and exposure-response relationship of amatuximab, an anti-mesothelin monoclonal antibody, in patients with malignant pleural mesothelioma and its application in dose selection. *Cancer Chemother Pharmacol.* 2016;77(4):733-43.
62. Jonsson EN, Xie R, Marshall SF, Arends RH. Population pharmacokinetics of tanezumab in phase 3 clinical trials for osteoarthritis pain. *Br J Clin Pharmacol.* 2016;81(4):688-99.
63. Kloft C, Graefe EU, Tanswell P, Scott AM, Hofheinz R, Amelsberg A, et al. Population pharmacokinetics of sibrotuzumab, a novel therapeutic monoclonal antibody, in cancer patients. *Invest New Drugs.* 2004 Jan;22(1):39-52.

64. Kuester K, Kovar A, Lupfert C, Brockhaus B, Kloft C. Population pharmacokinetic data analysis of three phase I studies of matuzumab, a humanised anti-EGFR monoclonal antibody in clinical cancer development. *Br J Cancer*. 2008;98(5):900-6. doi: 10.1038/sj.bjc.6604265. Epub 2008 Mar 4.
65. Kuester K, Kovar A, Lupfert C, Brockhaus B, Kloft C. Refinement of the population pharmacokinetic model for the monoclonal antibody matuzumab: external model evaluation and simulations. *Clin Pharmacokinet*. 2009;48(7):477-87. doi: 10.2165/11313400-000000000-00000.
66. Long A, Chigutsa E, Wallin J. Population Pharmacokinetics of Necitumumab in Cancer Patients. *Clin Pharmacokinet*. 2016;56(5):505-14.
67. Ma P, Yang BB, Wang YM, Peterson M, Narayanan A, Sutjandra L, et al. Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. *J Clin Pharmacol*. 2009;49(10):1142-56. doi: 10.77/0091270009344989. Epub 2009 Sep 1.
68. Muralidharan KK, Kuesters G, Plavina T, Subramanyam M, Mikol DD, Gopal S, et al. Population Pharmacokinetics and Target Engagement of Natalizumab in Patients With Multiple Sclerosis. *J Clin Pharmacol*. 2017;57(8):1017-30.
69. Quartino AL, Hillenbach C, Li J, Li H, Wada RD, Visich J, et al. Population pharmacokinetic and exposure-response analysis for trastuzumab administered using a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. *Cancer Chemother Pharmacol*. 2016;77(1):77-88.
70. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015;42(2):188-202.
71. Wu B, Joshi A, Ren S, Ng C. The application of mechanism-based PK/PD modeling in pharmacodynamic-based dose selection of muM17, a surrogate monoclonal antibody for efalizumab. *J Pharm Sci*. 2006;95(6):1258-68. doi: 10.002/jps.20475.
72. Xu XS, Yan X, Puchalski T, Lonial S, Lokhorst HM, Voorhees PM, et al. Clinical Implications of Complex Pharmacokinetics for Daratumumab Dose Regimen in Patients With Relapsed/Refractory Multiple Myeloma. *Clin Pharmacol Ther*. 2017;101(6):721-4.
73. Mould DR, Davis CB, Minthorn EA, Kwok DC, Elliott MJ, Luggen ME, et al. A population pharmacokinetic-pharmacodynamic analysis of single doses of clenoliximab in patients with rheumatoid arthritis. *Clin Pharmacol Ther*. 1999 Sep;66(3):246-57.
74. Mould DR, Baumann A, Kuhlmann J, Keating MJ, Weitman S, Hillmen P, et al. Population pharmacokinetics-pharmacodynamics of alemtuzumab (Campath) in patients with chronic lymphocytic leukaemia and its link to treatment response. *Br J Clin Pharmacol*. 2007;64(3):278-91. Epub 2007 May 16.
75. Wiczling P, Rosenzweig M, Vaickus L, Jusko WJ. Pharmacokinetics and pharmacodynamics of a chimeric/humanized anti-CD3 monoclonal antibody, oteelixizumab (TRX4), in subjects with psoriasis and with type 1 diabetes mellitus. *J Clin Pharmacol*. 2010;50(5):494-506.
76. Scherer N, Dings C, Bohm M, Laufs U, Lehr T. Alternative Treatment Regimens With the PCSK9 Inhibitors Alirocumab and Evolocumab: A Pharmacokinetic and Pharmacodynamic Modeling Approach. *J Clin Pharmacol*. 2017;57(7):846-54.
77. Endres CJ, Salinger DH, Kock K, Gastonguay MR, Martin DA, Klekotka P, et al. Population pharmacokinetics of brodalumab in healthy adults and adults with psoriasis from single and multiple dose studies. *J Clin Pharmacol*. 2014;54(11):1230-8.
78. Kovalenko P, DiCioccio AT, Davis JD, Li M, Ardeleanu M, Graham N, et al. Exploratory Population PK Analysis of Dupilumab, a Fully Human Monoclonal Antibody Against IL-

- 4Ralpha, in Atopic Dermatitis Patients and Normal Volunteers. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(11):617-24.
79. Azzopardi N, Lecomte T, Ternant D, Boisdron-Celle M, Piller F, Morel A, et al. Cetuximab pharmacokinetics influences progression-free survival of metastatic colorectal cancer patients. *Clin Cancer Res*. 2011;17(19):6329-37.
80. Pointreau Y, Azzopardi N, Ternant D, Calais G, Paintaud G. Cetuximab Pharmacokinetics Influences Overall Survival in Patients With Head and Neck Cancer. *Ther Drug Monit*. 2017;38(5):567-72.
81. Thibault G, Paintaud G, Legendre C, Merville P, Coulon M, Chasseuil E, et al. CD25 blockade in kidney transplant patients randomized to standard-dose or high-dose basiliximab with cyclosporine, or high-dose basiliximab in a calcineurin inhibitor-free regimen. *Transpl Int*. 2016;29(2):184-95.
82. Shen T, James DE, Krueger KA. Population Pharmacokinetics (PK) and Pharmacodynamics (PD) Analysis of LY3015014, a Monoclonal Antibody to Protein Convertase Subtilisin/Kexin Type 9 (PCSK9) in Healthy Subjects and Hypercholesterolemia Patients. *Pharm Res*. 2017;34(1):185-92.
83. Struemper H, Chen C, Cai W. Population pharmacokinetics of belimumab following intravenous administration in patients with systemic lupus erythematosus. *J Clin Pharmacol*. 2013;53(7):711-20.
84. Zhang X, Peyret T, Gosselin NH, Marier JF, Imel EA, Carpenter TO. Population pharmacokinetic and pharmacodynamic analyses from a 4-month intradose escalation and its subsequent 12-month dose titration studies for a human monoclonal anti-FGF23 antibody (KRN23) in adults with X-linked hypophosphatemia. *J Clin Pharmacol*. 2016;56(4):429-38.
85. Zheng B, Yu XQ, Greth W, Robbie GJ. Population pharmacokinetic analysis of sifalimumab from a clinical phase IIb trial in systemic lupus erythematosus patients. *Br J Clin Pharmacol*. 2016;81(5):918-28.
86. Ternant D, Buchler M, Beneton M, Alvan G, Ohresser M, Touchard G, et al. Interindividual variability in the concentration-effect relationship of antilymphocyte globulins - a possible influence of FcgammaRIIIa genetic polymorphism. *Br J Clin Pharmacol*. 2008;65(1):60-8. Epub 2007 Jul 4.
87. Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):58-66.
88. Gibiansky L, Frey N. Linking interleukin-6 receptor blockade with tocilizumab and its hematological effects using a modeling approach. *J Pharmacokinet Pharmacodyn*. 2014;39(1):5-16.
89. Li H, Yu J, Liu C, Liu J, Subramaniam S, Zhao H, et al. Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response. *J Pharmacokinet Pharmacodyn*. 2017;44(5):403-14.
90. Li J, Zhi J, Wenger M, Valente N, Dmoszynska A, Robak T, et al. Population pharmacokinetics of rituximab in patients with chronic lymphocytic leukemia. *J Clin Pharmacol*. 2012;52(12):1918-26.
91. Gibiansky E, Gibiansky L, Carlile DJ, Jamois C, Buchheit V, Frey N. Population Pharmacokinetics of Obinutuzumab (GA101) in Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma and Exposure-Response in CLL. *CPT Pharmacometrics Syst Pharmacol*. 2014;2014(29):42.
92. Sun YN, Lu JF, Joshi A, Compton P, Kwon P, Bruno RA. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous

- weekly dosing in psoriasis subjects. *J Clin Pharmacol*. 2005;45(4):468-76. doi: 10.1177/0091270004272731.
93. Cosson VF, Ng VW, Lehle M, Lum BL. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. *Cancer Chemother Pharmacol*. 2014;73(4):737-47.
94. Bernadou G, Campone M, Merlin JL, Gouilleux-Gruart V, Bachelot T, Lokiec F, et al. Influence of tumour burden on trastuzumab pharmacokinetics in HER2 positive non-metastatic breast cancer. *Br J Clin Pharmacol*. 2016;81(5):941-8.
95. Bruno R, Washington CB, Lu JF, Lieberman G, Banken L, Klein P. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol*. 2005 Oct;56(4):361-9. Epub 2005 May 3.
96. Blasco H, Chatelut E, de Bretagne IB, Congy-Jolivet N, Le Guellec C. Pharmacokinetics of rituximab associated with CHOP chemotherapy in B-cell non-Hodgkin lymphoma. *Fundam Clin Pharmacol*. 2009;23(5):601-8. doi: 10.1111/j.472-8206.2009.00714.x. Epub 2009 Jul 29.
97. Regazzi MB, Iacona I, Avanzini MA, Arcaini L, Merlini G, Perfetti V, et al. Pharmacokinetic behavior of rituximab: a study of different schedules of administration for heterogeneous clinical settings. *Ther Drug Monit*. 2005;27(6):785-92.
98. Tout M, Casasnovas O, Meignan M, Lamy T, Morschhauser F, Salles G, et al. Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: a Lymphoma Study Association report. *Blood*. 2017;129(19):2616-23.
99. Lioger B, Edupuganti SR, Mulleman D, Passot C, Desvignes C, Bejan-Angoulvant T, et al. Antigenic burden and serum IgG concentrations influence rituximab pharmacokinetics in rheumatoid arthritis patients. *Br J Clin Pharmacol*. 2017;83(8):1773-81.
100. Ng CM, Bruno R, Combs D, Davies B. Population pharmacokinetics of rituximab (anti-CD20 monoclonal antibody) in rheumatoid arthritis patients during a phase II clinical trial. *J Clin Pharmacol*. 2005 Jul;45(7):792-801.
101. Aubourg A, Picon L, Lecomte T, Bejan-Angoulvant T, Paintaud G, Ternant D. A robust estimation of infliximab pharmacokinetic parameters in Crohn's disease. *Eur J Clin Pharmacol*. 2015;71(12):1541-2.
102. Brandse JF, Mould D, Smeekes O, Ashruf Y, Kuin S, Strik A, et al. A Real-life Population Pharmacokinetic Study Reveals Factors Associated with Clearance and Immunogenicity of Infliximab in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2017;23(4):650-60.
103. Buurman DJ, Maurer JM, Keizer RJ, Kosterink JG, Dijkstra G. Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice. *Aliment Pharmacol Ther*. 2015;42(5):529-39.
104. Dotan I, Ron Y, Yanai H, Becker S, Fishman S, Yahav L, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014;20(12):2247-59.
105. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther*. 2011;33(7):946-64.
106. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009 Dec;65(12):1211-28.
107. Passot C, Mulleman D, Bejan-Angoulvant T, Aubourg A, Willot S, Lecomte T, et al. The underlying inflammatory chronic disease influences infliximab pharmacokinetics. *MAbs*. 2016;8(7):1407-16.

108. Ternant D, Arnoult C, Pugniere M, Dhommee C, Drocourt D, Perouzel E, et al. IgG1 Allotypes Influence the Pharmacokinetics of Therapeutic Monoclonal Antibodies through FcRn Binding. *J. Immunol.* 2016;196(2):607-13. doi: 10.4049/jimmunol.1501780. Epub 2015 Dec 18.
109. Ternant D, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit.* 2008;30(4):523-9. doi: 10.1097/FTD.0b013e318180e300.
110. Ternant D, Berkane Z, Picon L, Gouilleux-Gruart V, Colombel JF, Allez M, et al. Assessment of the Influence of Inflammation and FCGR3A Genotype on Infliximab Pharmacokinetics and Time to Relapse in Patients with Crohn's Disease. *Clin Pharmacokinet.* 2015;54(5):551-62.
111. Ternant D, Ducourau E, Perdriger A, Corondan A, Le Goff B, Devauchelle-Pensec V, et al. Relationship between inflammation and infliximab pharmacokinetics in rheumatoid arthritis. *Br J Clin Pharmacol.* 2014;78(1):118-28.
112. Ternant D, Mulleman D, Degenne D, Willot S, Guillaumin JM, Watier H, et al. An enzyme-linked immunosorbent assay for therapeutic drug monitoring of infliximab. *Ther Drug Monit.* 2006 Apr;28(2):169-74.
113. Ternant D, Mulleman D, Lauferon F, Vignault C, Ducourau E, Wendling D, et al. Influence of methotrexate on infliximab pharmacokinetics and pharmacodynamics in ankylosing spondylitis. *Br J Clin Pharmacol.* 2011;2011(22):1365-2125.
114. Xu Z, Seitz K, Fasanmade A, Ford J, Williamson P, Xu W, et al. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol.* 2008 Jun;48(6):681-95.
115. Mostafa NM, Nader AM, Noertersheuser P, Okun M, Awni WM. Impact of immunogenicity on pharmacokinetics, efficacy and safety of adalimumab in adult patients with moderate to severe chronic plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2017;31(3):490-7.
116. Nader A, Beck D, Noertersheuser P, Williams D, Mostafa N. Population Pharmacokinetics and Immunogenicity of Adalimumab in Adult Patients with Moderate-to-Severe Hidradenitis Suppurativa. *Clin Pharmacokinet.* 2017;56(9):1091-102.
117. Ternant D, Ducourau E, Fuzibet P, Vignault C, Watier H, Lequerre T, et al. Pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis. *Br J Clin Pharmacol.* 2015;79(2):286-97.
118. Ternant D, Karmiris K, Vermeire S, Desvignes C, Azzopardi N, Bejan-Angoulvant T, et al. Pharmacokinetics of adalimumab in Crohn's disease. *Eur J Clin Pharmacol.* 2015;71(9):1155-7.
119. Ternant D, Paintaud G, Trachtman H, Gipson DS, Joy MS. A possible influence of age on absorption and elimination of adalimumab in focal segmental glomerulosclerosis (FSGS). *Eur J Clin Pharmacol.* 2016;72(2):253-5.
120. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther.* 2003 Jun;25(6):1700-21.
121. Berends SE, Strik AS, Van Selm JC, Lowenberg M, Ponsioen CY, D'Haens GR, et al. Explaining Interpatient Variability in Adalimumab Pharmacokinetics in Patients With Crohn's Disease. *Ther Drug Monit.* 2018;40(2):202-11.
122. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis.* 2015;21(4):783-92.

123. Vande Castele N, Mould DR, Coarse J, Hasan I, Gils A, Feagan B, et al. Accounting for Pharmacokinetic Variability of Certolizumab Pegol in Patients with Crohn's Disease. *Clin Pharmacokinet*. 2017;56(12):1513-23.
124. Wade JR, Parker G, Kosutic G, Feagen BG, Sandborn WJ, Laveille C, et al. Population pharmacokinetic analysis of certolizumab pegol in patients with Crohn's disease. *J Clin Pharmacol*. 2015;55(8):866-74.
125. Hu C, Xu Z, Zhang Y, Rahman MU, Davis HM, Zhou H. Population approach for exposure-response modeling of golimumab in patients with rheumatoid arthritis. *J Clin Pharmacol*. 2011;51(5):639-48.
126. Xu Z, Vu T, Lee H, Hu C, Ling J, Yan H, et al. Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. *J Clin Pharmacol*. 2009;49(9):1056-70. doi: 10.1177/0091270009339192. Epub 2009 Jul 17.
127. Xu ZH, Lee H, Vu T, Hu C, Yan H, Baker D, et al. Population pharmacokinetics of golimumab in patients with ankylosing spondylitis: impact of body weight and immunogenicity. *Int*. 2010;48(9):596-607.
128. Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, et al. Pharmacokinetics and safety of golimumab, a fully human anti-TNF-alpha monoclonal antibody, in subjects with rheumatoid arthritis. *J Clin Pharmacol*. 2007 Mar;47(3):383-96.
129. Morell A, Terry WD, Waldmann TA. Metabolic properties of IgG subclasses in man. *J Clin Invest*. 1970 Apr;49(4):673-80.
130. Caulet M, Lecomte T, Bouche O, Rollin J, Gouilleux-Gruart V, Azzopardi N, et al. Bevacizumab Pharmacokinetics Influence Overall and Progression-Free Survival in Metastatic Colorectal Cancer Patients. *Clin Pharmacokinet*. 2016;55(11):1381-94.
131. Lu D, Girish S, Gao Y, Wang B, Yi JH, Guardino E, et al. Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates. *Cancer Chemother Pharmacol*. 2014;74(2):399-410.
132. Jodele S, Fukuda T, Mizuno K, Vinks AA, Laskin BL, Goebel J, et al. Variable Eculizumab Clearance Requires Pharmacodynamic Monitoring to Optimize Therapy for Thrombotic Microangiopathy after Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2016;22(2):307-15.
133. Gupta M, Lorusso PM, Wang B, Yi JH, Burris HA, 3rd, Beeram M, et al. Clinical implications of pathophysiological and demographic covariates on the population pharmacokinetics of trastuzumab emtansine, a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. *J Clin Pharmacol*. 2012;52(5):691-703.
134. Stroh M, Winter H, Marchand M, Claret L, Eppler S, Ruppel J, et al. Clinical Pharmacokinetics and Pharmacodynamics of Atezolizumab in Metastatic Urothelial Carcinoma. *Clin Pharmacol Ther*. 2017;102(2):305-12.
135. Mo G, Baldwin JR, Luffer-Atlas D, Ilaria RL, Jr., Conti I, Heathman M, et al. Population Pharmacokinetic Modeling of Olaratumab, an Anti-PDGFRalpha Human Monoclonal Antibody, in Patients with Advanced and/or Metastatic Cancer. *Clin Pharmacokinet*. 2018;57(3):355-65.
136. Ahamadi M, Freshwater T, Prohn M, Li CH, de Alwis DP, de Greef R, et al. Model-Based Characterization of the Pharmacokinetics of Pembrolizumab: A Humanized Anti-PD-1 Monoclonal Antibody in Advanced Solid Tumors. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):49-57.

137. Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma. *J Clin Pharmacol*. 2014;54(10):1108-16.
138. Yao Z, Hu C, Zhu Y, Xu Z, Randazzo B, Wasfi Y, et al. Population Pharmacokinetic Modeling of Guselkumab, a Human IgG1 λ Monoclonal Antibody Targeting IL-23, in Patients with Moderate to Severe Plaque Psoriasis. *J Clin Pharmacol*. 2018;2018(17).
139. Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. *Arthritis Rheum*. 2006 Dec;54(12):3782-9.
140. Wolbink GJ, Voskuyl AE, Lems WF, de Groot E, Nurmohamed MT, Tak PP, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2005 May;64(5):704-7.
141. Elliott MJ, Feldmann M, Maini RN. TNF alpha blockade in rheumatoid arthritis: rationale, clinical outcomes and mechanisms of action. *Int J Immunopharmacol*. 1995;17(2):141-5.
142. Elliott MJ, Maini RN. Anti-cytokine therapy in rheumatoid arthritis. *Baillieres Clin Rheumatol*. 1995;9(4):633-52.
143. Maini RN, Elliott MJ, Brennan FM, Williams RO, Chu CQ, Paleolog E, et al. Monoclonal anti-TNF alpha antibody as a probe of pathogenesis and therapy of rheumatoid disease. *Immunol Rev*. 1995 Apr;144:195-223.
144. Han K, Peyret T, Quartino A, Gosselin NH, Gururangan S, Casanova M, et al. Bevacizumab dosing strategy in paediatric cancer patients based on population pharmacokinetic analysis with external validation. *Br J Clin Pharmacol*. 2016;81(1):148-60.
145. Hua F, Ribbing J, Reinisch W, Cataldi F, Martin S. A pharmacokinetic comparison of anrukizumab, an anti-IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. *Br J Clin Pharmacol*. 2015;80(1):101-9.
146. Zhu M, Gosselin NH, Kuchimanchi M, Johnson J, McCaffery I, Mouksassi MS, et al. Differential Pharmacokinetics of Ganitumab in Patients With Metastatic Pancreatic Cancer Versus Other Advanced Solid Cancers. *Clin Pharmacol Drug Dev*. 2013;2(4):367-78.
147. Azzopardi N, Dupuis-Girod S, Ternant D, Fargeton AE, Ginon I, Faure F, et al. Dose-response relationship of bevacizumab in hereditary hemorrhagic telangiectasia. *MAbs*. 2015;7(3):630-7.
148. Han K, Peyret T, Marchand M, Quartino A, Gosselin NH, Girish S, et al. Population pharmacokinetics of bevacizumab in cancer patients with external validation. *Cancer Chemother Pharmacol*. 2016;78(2):341-51.
149. Lu JF, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemother Pharmacol*. 2008;62(5):779-86. doi: 10.1007/s00280-007-0664-8. Epub 2008 Jan 19.
150. Turner DC, Navid F, Daw NC, Mao S, Wu J, Santana VM, et al. Population pharmacokinetics of bevacizumab in children with osteosarcoma: implications for dosing. *Clin Cancer Res*. 2014;20(10):2783-92.
151. Muller C, Murawski N, Wiesen MH, Held G, Poeschel V, Zeynalova S, et al. The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. *Blood*. 2012;119(14):3276-84.

152. Fischer SK, Yang J, Anand B, Cowan K, Hendricks R, Li J, et al. The assay design used for measurement of therapeutic antibody concentrations can affect pharmacokinetic parameters: Case studies. *MABs*. 2012;4(5):623-31. doi: 10.4161/mabs.20814. Epub 2012 Jul 23.
153. Gratacos J, Collado A, Filella X, Sanmarti R, Canete J, Llana J, et al. Serum cytokines (IL-6, TNF-alpha, IL-1 beta and IFN-gamma) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. *Br J Rheumatol*. 1994 Oct;33(10):927-31.
154. Manicourt DH, Triki R, Fukuda K, Devogelaer JP, Nagant de Deuxchaisnes C, Thonar EJ. Levels of circulating tumor necrosis factor alpha and interleukin-6 in patients with rheumatoid arthritis. Relationship to serum levels of hyaluronan and antigenic keratan sulfate. *Arthritis Rheum*. 1993;36(4):490-9.
155. Manicourt DH, Poilvache P, Van Egeren A, Devogelaer JP, Lenz ME, Thonar EJ. Synovial fluid levels of tumor necrosis factor alpha and oncostatin M correlate with levels of markers of the degradation of crosslinked collagen and cartilage aggrecan in rheumatoid arthritis but not in osteoarthritis. *Arthritis Rheum*. 2000;43(2):281-8. doi: 10.1002/529-0131(200002)43:2<281::AID-ANR7>3.0.CO;2-7.
156. Ferri N, Bellosta S, Baldessin L, Boccia D, Racagni G, Corsini A. Pharmacokinetics interactions of monoclonal antibodies. *Pharmacol Res*. 2016;111:592-9.
157. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispen T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis*. 2013;2013(10):2013-204172.
158. Baert F, Noman M, Vermeire S, Van Assche G, G DH, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003 Feb 13;348(7):601-8.
159. Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. *Blood*. 2002 Feb 1;99(3):754-8.
160. Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol*. 2003 Nov 1;21(21):3940-7. Epub 2003 Sep 15.
161. Zhang W, Gordon M, Schultheis AM, Yang DY, Nagashima F, Azuma M, et al. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. *J Clin Oncol*. 2007;25(24):3712-8.
162. Musolino A, Naldi N, Bortesi B, Pezzuolo D, Capelletti M, Missale G, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. *J Clin Oncol*. 2008;26(11):1789-96. doi: 10.200/JCO.2007.14.8957. Epub 2008 Mar 17.
163. Ternant D, Buchler M, Thibault G, Ohresser M, Watier H, Lebranchu Y, et al. Influence of FcgammaRIIIA genetic polymorphism on T-lymphocyte depletion induced by rabbit antithymocyte globulins in kidney transplant patients. *Pharmacogenet Genomics*. 2014;24(1):26-34.
164. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther*. 2002 May;301(2):418-26.
165. Scallon BJ, Trinh H, Nedelman M, Brennan FM, Feldmann M, Ghrayeb J. Functional comparisons of different tumour necrosis factor receptor/IgG fusion proteins. *Cytokine*. 1995 Nov;7(8):759-70.

166. Louis E, El Ghoul Z, Vermeire S, Dall'Ozzo S, Rutgeerts P, Paintaud G, et al. Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther.* 2004 Mar 1;19(5):511-9.
167. Louis EJ, Watier HE, Schreiber S, Hampe J, Taillard F, Olson A, et al. Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. *Pharmacogenet Genomics.* 2006 Dec;16(12):911-4.
168. Kut C, Mac Gabhann F, Popel AS. Where is VEGF in the body? A meta-analysis of VEGF distribution in cancer. *Br J Cancer.* 2007;97(7):978-85. doi: 10.1038/sj.bjc.6603923. Epub 2007 Oct 2.
169. Gibiansky L, Gibiansky E. Target-mediated drug disposition model for drugs that bind to more than one target. *J Pharmacokinet Pharmacodyn.* 2010;37(4):323-46.
170. Xin Y, Xiang H, Jin D, Theil FP, Joshi A, Damico-Beyer LA, et al. Population pharmacokinetic and pharmacodynamic modeling of MNRP1685A in cynomolgus monkeys using two-target quasi-steady-state (QSS) model. *J Pharmacokinet Pharmacodyn.* 2012;39(2):217-26.
171. Li L, Gardner I, Dostalek M, Jamei M. Simulation of monoclonal antibody pharmacokinetics in humans using a minimal physiologically based model. *Aaps J.* 2014;16(5):1097-109.
172. Darrouzain F, Bian S, Desvignes C, Bris C, Watier H, Paintaud G, et al. Immunoassays for Measuring Serum Concentrations of Monoclonal Antibodies and Anti-biopharmaceutical Antibodies in Patients. *Ther Drug Monit.* 2017;39(4):316-21.
173. Park WS, Han S, Lee J, Hong T, Won J, Lim Y, et al. Use of a Target-Mediated Drug Disposition Model to Predict the Human Pharmacokinetics and Target Occupancy of GC1118, an Anti-epidermal Growth Factor Receptor Antibody. *Basic Clin Pharmacol Toxicol.* 2017;120(3):243-9.
174. Davda JP, Dodds MG, Gibbs MA, Wisdom W, Gibbs J. A model-based meta-analysis of monoclonal antibody pharmacokinetics to guide optimal first-in-human study design. *MAbs.* 2014;6(4):1094-102.
175. Kamath AV. Translational pharmacokinetics and pharmacodynamics of monoclonal antibodies. *Drug Discov Today Technol.* 2016;22:75-83.
176. Passot C, Pouw MF, Mulleman D, Bejan-Angoulvant T, Paintaud G, Dreesen E, et al. Therapeutic Drug Monitoring of Biopharmaceuticals May Benefit From Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling. *Ther Drug Monit.* 2017;39(4):322-6.

8 Legends of the figures

Figure 1. Target-mediated drug disposition (TMDD) models used to describe the influence of antigen mass on antibody pharmacokinetics. A, base TMDD model, which necessitates, to be identifiable, dense sampling strategy of free antibody concentrations in the central compartment (C), target antigen (R) and antibody-antigen complex (RC) compartments; B, TMDD model under the quasi-steady-state approximation (see section 3.3.1); C, hypothesis of irreversible binding; D, Michaelis-Menten approximation; E, influence of antigen mass as a covariate on pharmacokinetic parameters; F, TMDD of cytotoxic antibody and target antigen expressed at the membrane of inflammatory cells. Because of the higher affinity of the V allotype of Fc γ RIIIA for the Fc portion of IgGs, the antibody-induced antibody-dependent cell cytotoxicity (ADCC) elimination rate (k_{ADCC}) may be higher in V/V patients than in F carriers, resulting to an increased target mediated antibody elimination. Abbreviations – C, concentration of free antibody in the central compartment; R, free target antigen amount; RC, antibody-antigen complex amount; $In(t)$, antibody infusion function; k_{10} , k_{12} , k_{21} elimination and transfer first-order rate constants; k_{syn} and k_{deg} , zero-order input and first-order output of target antigen rate constants, respectively; k_{on} and k_{off} , antibody and target second-order association and first-order dissociation rate constants, respectively; k_{int} , internalization (i.e. complex elimination) rate constant; K_{SS} , quasi-steady-state dissociation rate constant, V_M and K_M , maximum rate and Michaelis constants, respectively; COV, covariate; NK: natural killer cells; k_{ADCC} : infliximab-induced antibody-dependent cell cytotoxicity (ADCC) elimination rate constant.

Figure 2. Concentration-time target-mediated drug disposition (TMDD) pharmacokinetic profiles. Parameters that were used for simulations were central volume of distribution (V), first-order elimination (k_{10}) and transfer rate constants (k_{12} and k_{21}), endogenous zero-order production (k_{syn}) and first-order destruction (k_{deg}) rate constants, second-order and first order association rate constant of mAb to its target (k_{on}), dissociation rate constant the complex (k_{off}), respectively, and first-order complex destruction rate constant (k_{int}). Base parameter values were taken from TMDD kinetics of TRX1 an anti-CD4 monoclonal antibody.^[33] A, TMDD profiles according to increasing (solid to dotted lines) target antigen amount (R) from 1 to 20 (arbitrary units); B, TMDD profiles according to increasing dose (D, solid to dotted lines) of therapeutic antibody from 100 to 1000 mg; C, visualization of the four phases of TMDD kinetics, (i) rapid 2-order decay due to the association of antibody to target, (ii) slow 1-order decay related to unbound mAb elimination and saturated target, (iii) a mixed-order re-increase of elimination rate due to unsaturated targets and (iv) terminal decay driven by k_{off} and k_{int} . Up and bottom curves correspond to extreme cases were antibody in stoichiometric excess compared to antigen mass, only phases (i) and (ii) are observable (up) and antibody in stoichiometric default compared to antigen mass; only phases (i) and (iv) are observable (bottom); D, TMDD profiles according to increasing internalization rate constant (k_{int} , solid to dotted lines) from 0.0393 to 3.93 day⁻¹.

Figure 3. Dose-concentration-response relationship for monoclonal antibodies (mAbs). Arrows and truncated lines represent stimulation and inhibition relationships between boxes, respectively. Increased mAb concentrations decrease antigen amounts and increased antigen amounts increase disease activity. Because antigen mass accelerates mAb elimination, high antigen amounts lead to low mAb concentrations. Biomarker levels should be correlated to antigenic mass and disease activity. However, disease activity and biomarker levels may be associated with factors other than antigen mass. Antigen may be expressed in several tissues, e.g. circulating and cellular antigen mass. Because of the higher affinity of the V allotype of Fc γ RIIIA for the Fc portion of

IgGs, the antibody-induced antibody-dependent cell cytotoxicity elimination rate may be higher in V/V patients than in F carriers, resulting to an increased target mediated antibody elimination.