



Monoclonal antibodies: Pharmacokinetics as a basis for new dosage regimens?

J-R Azanza, B Sádaba and A Gómez-Guiu

Abstract

Complete monoclonal IgG antibodies which are in use in clinical practice share some pharmacological properties resulting in high concentrations in plasma. This fact is reflected in their low volumes of distribution, which can also be correlated with a high molecular weight and water solubility. This feature allows a novel approach to be applied to the dosing schedule for this group of drugs with fixed doses being used instead of the initially developed weight- or body surface-adjusted dosing schedules. In addition, the development of a new formulation containing hyaluronidase allows a subcutaneous route of administration to be used, because hyaluronidase creates a space in the subcutaneous tissue that helps antibody absorption. This method requires higher doses, but has allowed testing the feasibility of administering a fixed dose, with no individual dose adjustments based on weight or body surface. Moreover, loading doses are not needed, because the first dose results, within 3 weeks, in minimum concentrations that are higher than effective concentrations.

Keywords

Monoclonal antibodies, pharmacokinetics, hyaluronidase, route of administration, dosage

Introduction

Clinicians' knowledge about the drugs they prescribe is usually limited to the main drug indications and recommended dosage, and just a few aspects on the final prescription tailoring. This seems to affect all drug classes; the biological agents, in spite of having been only introduced in recent years, do not seem to be exempt from such a problem.

The present article sets out to discuss, from a practical point of view for the prescribing practitioner, the implications of existing pharmacokinetic data on therapeutic use of an important class of biological agents, monoclonal antibodies (mAb). For such a challenging aim, we will focus on trastuzumab and rituximab and will take both mAbs as examples illustrating the usefulness of pharmacokinetics. From a pharmacokinetic point of view, both trastuzumab and rituximab are particularly attractive because of their novel recently developed subcutaneous (SC) formulations that will result in a change of dose adjustment methods from previous body weight- or surface area-based dosage to the currently proposed fixed dose pattern. The new dosing schedules can cause a number of doubts that can be

clarified by means of the pharmacokinetic properties of both mAb. The main parameters are summarized in Table 1.

Chemical structure and some pharmacodynamic concepts

Virtually all currently used mAb are IgG-type immunoglobulins, most of them consisting of an entire molecule, though a few therapeutically used mAb, such as ranibizumab, consist of only a fraction of the immunoglobulin molecule; some others are fusion proteins, with an immunoglobulin providing the constant portion and the variable portion having been replaced by different components. As expected, drugs consisting in an entire immunoglobulin share a number of chemical, pharmacodynamic and pharmacokinetic properties.^{1,2}

Department of Clinical Pharmacology, Clínica Universidad de Navarra, Pamplona, Spain

Corresponding author:

J-R Azanza, Department of Clinical Pharmacology, Clínica Universidad de Navarra, Pamplona, Spain.
Email: jrazanza@unav.es

Table 1. Pharmacokinetic parameters of rituximab and trastuzumab. Intravenous administration.¹⁹

	Rituximab ¹⁸	Trastuzumab ¹⁹
Dose	375 mg/m ²	2 mg/kg
AUC	118.23 ± 53.4 mg/l h	182 ± 21 mg/l h
t _{1/2}	387 ± 188.9 h	–
C _{max}	92.1 ± 34 mg/l	43.4 ± 8.5 mg/l
Cl	0.004 ± 0.064 ml/day	11.1 ± 1.4 ml/day kg
V _{ss}	11.6 ± 3.2 l	52.6 ± 21.2 ml/kg

AUC: area under the curve; Cl: clearance; t_{1/2}: elimination half-life; V_{ss}: distribution volume.

Chemical structure reflects a typical immunoglobulin architecture consisting of heavy and light chains with variable regions (recognition and antigen- or drug target-binding site) and a constant region that can bind to specific cell receptors, i.e. FcR γ and FcRn, contributing to drug response features and to drug transit throughout the body.

Variable region binding to its drug target results in some typical effects, such as complement-mediated cytotoxicity, activation of apoptotic mechanisms, and, through its binding to Fc γ receptor, causes cell-mediated cytotoxicity resulting in phagocytosis. Thus, immunoglobulin variable region binding to its target results in target destruction, and partially destroys also the immunoglobulin itself.^{3–8}

This is a very relevant process helping to explain the fact that both drug effect strength and drug clearance rate depend sometimes on the available amount of drug target.

Immunoglobulins are a major element in human body, with several non-antigen-depending mechanisms allowing its homeostatic regulation. Pharmacologically developed mAbs have similar functions and structure, and as a consequence they share such protective mechanisms against lysosomal proteolysis. Such protection is mediated by a specific kind of receptors, the FcRn, that are usually located inside the cell and can bind to immunoglobulins in an acidic pH environment. Bound immunoglobulins are able to transit intracellularly and avoid lysosomal proteolysis. Later on, when a neutral pH is present, immunoglobulins are released to extracellular environment. There, immunoglobulins can enter blood vessels through transcytosis and are ready again to produce their pharmacological effect.^{9–15}

This sophisticated homeostatic system is used by all immunoglobulins, either natural or pharmacologically developed, by means of their constant region. Such findings explain two main properties of mAb. Firstly, they show an unusually long residence time in the body, not to be expected for most proteins; thus, elimination half-life of mAbs is usually very long, close or even

longer than 21 days. Secondly, homeostatic mechanisms explain the presence of mAbs in bloodstream after a local administration.¹⁶

Finally, IgG immunoglobulins have a very high molecular weight (about 150 kDa) and are very water soluble. Such properties are responsible for their unique pharmacokinetic behaviour.^{1,17}

Pharmacokinetics

Due to their high molecular weight and water solubility, mAbs are almost exclusively distributed to vascular compartment, with only a small fraction reaching extracellular fluid. Transit from vascular compartment to extracellular compartment can be caused either by extravasation or by endocytosis or pinocytosis. However, a FcRn receptor-mediated transit mechanism in vascular endothelium cannot be excluded.

This conclusion can be easily established when peak plasma concentrations (C_{max}) achieved after intravenous (IV) administration of conventional doses are considered.

Distribution volume can be estimated by dividing dose by peak plasma concentration. As an example, using rituximab pharmacokinetic parameters (Table 1), a C_{max} value of 92 μ g/ml has been described after the administration of a 375 mg/m² IV dose in patients with lymphoma.¹⁸ Based on such data, distribution volume can be estimated by dividing dose by C_{max}; in other words, if an amount of drug of 92 μ g is present in 1 ml body water, we aim at determining the amount of water containing the 375 mg/m² dose that has been administered; that is a rituximab distribution volume of 7–8 l.

C_{max} values for trastuzumab are 43.2 mg/l after a 2 mg/kg dose. Thus, for an average body weight of 70 kg, the estimated distribution volume is about 3–4 l.¹⁹

Interpretation of these values is not difficult. In adults, body water content is distributed as follows: vascular volume 4–5 l and, extracellular fluid 14–20 l, with intracellular fluid containing the additional amount to reach 70% of body weight. A comparison of these figures with the estimated distribution volume values clearly shows that rituximab and trastuzumab are almost exclusively distributed to bloodstream. This finding becomes very significant when deciding whether or not a dose adjustment based on patient's body weight or surface area is needed.

The typically low distribution volume of immunoglobulins leads to one of the key concepts: no body weight or surface area-based adjustments are necessary for immunoglobulin doses because, in practical terms, the volume of fluid in bloodstream does not depend on body weight. In other words, vascular water amounts

are very similar in severely obese and thin people. Thus, weight alterations effect on the distribution and the levels of mAb being achieved is scarcely relevant, and dose adjustments based on body weight or surface area are questionable. In a simulation study of mAb dosing based on body weight or body surface area, Blai et al.²⁰ have also recommended the use of a fixed dose regimen when administration of such agents is started.

Intravenous trastuzumab doses have been systematically adjusted according to body weight, but this will change in the near future with a new SC formulation that has been developed for fixed dose administration. In fact, the change was to be expected, taking into account the findings from a number of studies that have suggested a scarcely relevant influence of weight on pharmacokinetic variability.^{21,22}

Intravenous rituximab was developed using body surface area-adjusted doses, with differing dosages for each specific therapeutic use: follicular lymphoma 375 mg/m², chronic lymphocytic leukaemia 500 mg/m². Later on, after a scarce influence of weight/height on pharmacokinetic variability was confirmed, the dose pattern (1000 mg) for a subsequently developed indication, i.e. rheumatoid arthritis, did no longer include a body weight adjustment.²³ Over the years, several studies^{24,25} demonstrated that body weight- or surface area-based adjustment do not reduce in a significant way the pharmacokinetic variability, which is regularly observed, regardless of dose adjustments.^{26–33}

Stating that a dosing pattern that has been used over many years with a good efficacy and safety profile may be unnecessary begets some uncertainty, particularly because overdosage or underdosage could have occurred in patients with extreme body weight values. Some additional data are reassuring, though. Homeostasis for any immunoglobulin is under physiological control by very strict processes that allow an exponential clearance of a protein when blood levels are increased.¹³ Furthermore, it should be considered that C_{max} values, even when these two drugs are administered to obese patients using a body weight- or body surface area-dose adjustment, are substantially lower than physiological levels present in plasma. It should be remembered that physiological immunoglobulin concentrations in plasma are between 12 and 20 mg/ml.¹³ These facts allowed overdosed therapies to be used with an extremely good tolerability in some patients. The lack of relationship between administered dose and side effects incidence and/or severity is a reflection of the absence of such a clear-cut relationship.^{34–37}

The development of an entire clinical research process with such a dosage pattern can seem surprising taking into account it could be presumed that there was no need for it. However, the existing historical

situation when such drugs were investigated must be considered,^{38–41} because they were the first in a new class of drugs with a very specific and, at the same time, poorly known mechanism of action, which necessarily resulted in a substantial fear of adverse effects. Therefore, controlling pharmacokinetic variability was a real need and, among other measures, dose adjustment was considered an unavoidable practice.

A better understanding of this kind of agents, their side effects and their pharmacokinetics, based on a number of papers over the last years, has allowed other dosage patterns to be investigated, with their results providing an easier and more comfortable use.

Elimination

As for any other immunoglobulin, mAbs elimination occurs through proteolysis and splitting into peptides, smaller size proteins and amino acids that are partially re-utilized or excreted through other pathways. Several systems are involved in the elimination process, such as macrophages and monocytes that are able to internalize the immunoglobulin once it is bound to FC- γ receptors. Internalization is followed by the action of lysosomal enzymes resulting in immunoglobulin breakdown.^{42–44} This mechanism can be important because of its strength, with several polymorphisms having been described that could possibly have an impact on pharmacodynamic features.

A similar mechanism can be found in cells with immunoglobulin receptors that are used as drug targets, because after immunoglobulin binding to its target by means of the variable region, internalization followed breakdown resulting from lysosomal enzyme action would occur.^{5,45,46} In the presence of high concentrations of the target protein, such a mechanism could result in clearance and distribution changes.³³

The excretion of immunoglobulins in general and mAbs in particular by the human body is very slow, as reflected by their clearance values that are 0.68^{19,47,48} and 0.73 ml/min¹⁸ for trastuzumab and rituximab, respectively. Elimination half-life is accordingly high, as observed for usual physiological immunoglobulins, due to the presence of the FcRn-mediated IgG recirculation system, as described earlier.

Although there are several methods available to calculate elimination half-life, an easy way to estimate drug half-life is based on the use of the plasma concentration curve. The curve for rituximab¹⁸ will be used as an illustrative example (Figure 1). The final part of the curve describing drug elimination rate is particularly important. Elimination half-life is defined as the time required to achieve a 50% reduction in drug levels. A concentration value easy to divide by two is identified, and both values are then marked on y-axis;

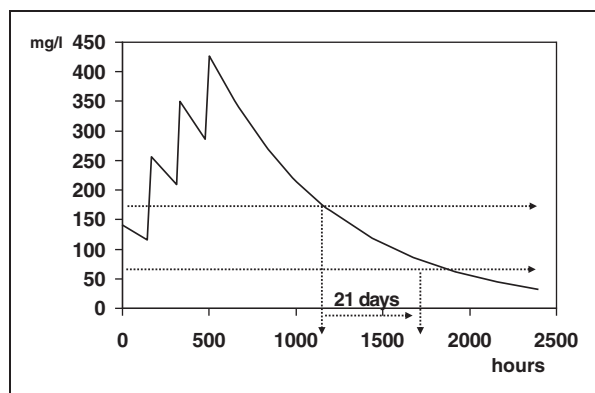


Figure 1. Plasma concentration curve for rituximab. Based on data from Tobinai et al.¹⁸

corresponding times are located on x-axis, and perpendicular lines are drawn. The difference in time values on x-axis is an estimate of the elimination half-life. In the example, rituximab elimination half-life is about 21 days.

Half-life is mainly used to estimate the time to drug disappearance from the body. After each half-life period of time, i.e. 21 days, plasma level is reduced by 50%. The remaining drug level can be estimated after each 21-day period until a negligible level (at least as compared with initial level) is achieved. As a general rule, it is widely accepted that after five half-life periods of time, more than 99% of the administered dose has been eliminated; thus, the remaining drug level can be confidently considered irrelevant. This is a very important concept, because, when drug effects are directly related to plasma levels, the time at which they will disappear can be estimated.

However, duration of efficacy based on the elimination half-life of a drug according to its plasma levels is usually different from duration of drug administration intervals (much shorter intervals are commonly used). The reason for such an apparent anachronism is the need to avoid administering very high doses that could result in a potentially dangerous C_{max} value. Thus, the dose for a period is usually divided in two or more fractions containing a similar amount of drug to be given at similar intervals along the administration period. Dose fractioning prevents the problems resulting from too high C_{max} values, but can also result in a progressively increasing plasma level being attained with each successive dose. The first drug dose produces a C_{max} value starting from a previous drug level of zero, whereas the second dose (that has been given before a zero level is restored) will start providing plasma concentrations when drug concentrations resulting from previous dose are still present. The addition of both concentrations then results in a higher C_{max} value. The sequence is repeated over and over

each time the same dose and administration conditions are used. However, once a number of doses have been given (Figure 1) plasma levels become virtually constant. A balance between doses and concentrations seems to have been reached; this is called steady state. From this point on each dose results in the same sequence of concentrations, and accordingly, the same effects are obtained. Steady state conditions are achieved after dosage has been maintained unchanged for five elimination half-life periods of the drug, regardless of the number of doses being given during this period.

In order to reach steady state conditions as soon as possible, a starting dose higher than subsequent doses can be administered (the 'loading dose').

As previously mentioned, mAbs have very high half-life periods (up to 21 days); thus, steady state conditions are reached at 105 days, or 15 weeks, with a continuous administration of a mAb at the usual 2–4-week intervals. Over that time, drug levels are usually checked after each dose to verify that each concentration is higher than previous ones, resulting in an uninterrupted succession until steady state is reached.

Absorption

Absorption pharmacokinetics evaluate the rate and the total amount of drug entering the body and becoming available to produce its pharmacological effect, when being given by an extravascular route of administration. The three most commonly used parameters to describe absorption are C_{max} ; the time until C_{max} is reached after drug administration (t_{max}), and bioavailability (f), i.e. the proportion (%) of the administered drug amount that is available in bloodstream to be distributed and produce its pharmacological effects.

As discussed earlier, mAbs are water-soluble macromolecules; therefore, their absorption after an SC or intramuscular (IM) administration is low. Moreover, the amount of drug to be given in a dose must be previously diluted in a very high volume of solution, which prevents in many cases using such routes of administration.⁴⁹

Human recombinant hyaluronidase⁵⁰ is able to release hyaluronic acid within the administration area.^{51,52} Hyaluronic acid produces channels (up to 200 nm in size),⁴⁹ which allows large size molecules and high volume of solutions to be absorbed. Additionally, hyaluronidase has a short half-life⁵³ and new hyaluronic acid is rapidly produced by the body, thus allowing a local restoration to be achieved in less than 24 h. The enzyme has been used to obtain an appropriate bioavailability after SC administration of rituximab or trastuzumab.

Drug bioavailability estimation requires the comparison of a pharmacokinetic parameter for the various drug formulations, the IV route being the one used as a reference. The best single parameter to describe the global behaviour of a drug in the body is the area under the curve (AUC) of drug concentrations, a numerical value for the area expressed in the units used in the axes, i.e. concentration–time units. AUC provides a global quantitative estimate for the pharmacokinetic behaviour because the effects of drug absorption, distribution and elimination magnitudes and rates are all included.

Drug bioavailability is obtained dividing AUC of a test formulation by the AUC after IV administration, preferably with a similar dose and over the same time interval, and then multiplying by 100. A 100% bioavailability indicates that both formulations have identical AUC.

The bioavailability of the new SC formulations of trastuzumab⁵⁴ and rituximab³⁶ has been investigated in several studies. SC tolerability for both formulations was similar to the intravenous administration tolerability. With a 6 mg/kg dose, the bioavailability of a SC trastuzumab formulation was 84%, whereas with a 8 mg/kg dose bioavailability reached 122 and 116% in healthy women and in patients, respectively, and this was the dose selected for development in confirmative clinical trials. A complex pharmacokinetic/pharmacodynamic process was needed to convert it to a fixed dose, corresponding approximately to the 8 mg/kg dose multiplied by a conventional body weight of 70 kg, i.e. a 560 mg fixed dose or 600 mg after rounding.

Intravenous route of administration has been systematically used for trastuzumab, with a loading dose equal to a double maintenance dose to reach an effective level (minimal drug concentration [Cmin] > 20 mg/l) from the beginning of the treatment.⁵⁵ The same schedule has been applied for both recommended dosages: loading dose 4 mg/kg and maintenance dose 2 mg/kg or loading dose 8 mg/kg and maintenance dose 6 mg/kg, respectively.⁴⁷ With the new SC formulation, no loading dose is used, because the proposed 600 mg dose produces a Cmin close to 30 mg/l with the first administration, thus surpassing the proposed minimal suitable value from the start.^{22,54,56}

Due to the two previously discussed characteristics, there is no need for an initial loading dose for SC administration, and successive doses result in progressively increasing levels until a steady state is achieved after five half-life periods, about 105 days. Steady state drug levels close to 60 mg/l have been reported as Cmin value.

A rituximab study with a 375 mg/m² SC dose showed a bioavailability of 49 and 67% when the drug was administered every 2 or 3 months,

respectively, in patients with lymphoma. The most favourable profile was obtained with a 800 mg/m² dose, and a 106 and 113% bioavailability was reached.³⁶ Specific calculations were needed to convert it in a non-adjusted dose, which was based on pharmacokinetic information obtained in the study and integrated in a population model to estimate the Cmin and AUC values that could be obtained with different dosage schedules for SC administration. A 1400 mg SC dose resulted in Cmin and AUC values non-inferior to the ones resulting from a 375 mg/m² IV dose in more than 80 and 95% of simulations, respectively.⁵⁷

The recommended SC schedule for rituximab includes an initial IV dose. Its purpose is not pharmacokinetic, because SC formulation results in an effective Cmin after the first dose. The recommendation is based on safety reasons. The most dangerous adverse effect of rituximab is the cytokine release syndrome, and a semi-slow IV infusion for the first dose helps to ensure an early recognition of the symptoms and prompt use of timely therapeutic measures, such as dosing delay or even early drug discontinuation; such measures would not be possible with the SC route.

Conclusion

In conclusion, daily dose selection for trastuzumab and rituximab SC formulations (i.e. 600 and 1400 mg, respectively) is based on several well-supported arguments: initial Cmin are higher than those reached with IV administration and clearly exceed Cmin values associated to a threshold for efficacy; AUC values are similar or even slightly higher than those observed with IV administration. Such results are obtained with an appropriate tolerability profile.

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Conflict of interest

None declared.

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