MONOCLONAL ANTIBODIES: CLINICAL PHARMACOLOGY KNOWLEDGE IN SUPPORT OF FIH AND EARLY DEVELOPMENT

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Several monoclonal antibody (mAbs) drugs have been approved, or are at the late stage of clinical development within various therapeutic indications. The amount of mAbs making it to the market will continue to increase thanks to their characteristics, including good solubility and stability, long persistence in the body, high selectivity and specificity of action, and low risk of toxic metabolites.

However, mAbs still have complex pharmacokinetic (PK) and pharmacodynamic (PD) properties compared to small chemical molecules. These include poor bioavailability, slow distribution, both linear- and non-linear elimination processes, and other factors influencing PK and PD such as immune reactions/immunogenicity.

Analyses of a new compound's PK and PD properties is an essential step in the early phases of drug development, and this process is still more complicated for mAbs.

Before planning a first-in-human (FIH) study, robust pre-clinical data should be available providing sufficient insight into the full PD pathways, and used to select the most appropriate animal species from both PK/PD and safety considerations. Challenging steps in designing FIH with mAb drugs therefore remain, and include the selection of safe and appropriate starting dose; the choice of dose escalation steps to achieve the goal of FIH study; the planning of sufficient and correct follow-up procedures; and the safety monitoring necessary, considering both the short term infusion related reactions and delayed PD effects.

In addition, due to incidents in the past, authorities look more rigorously towards mAbs, considering many of them as high-risk medicinal products. A sound early clinical development plan, including appropriate justifications, might help regulatory bodies with their evaluation of what they view as high-risk.

INTRODUCTION

Antibodies, also called immunoglobulins (Igs), are large proteins used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. The initial mAbs were generated from mouse and rat hybridomas. These first-generation antibodies had only limited clinical success because of their short half-lives and high immunogenicity. Several approaches have been developed to humanize these rodent antibodies, and technological advances during the past four decades have allowed mAbs to be developed and produces at commercial scale. The US Food and Drug administration (FDA) and the European Medicines Agency (EMA) have approved many mAbs in various therapeutic areas, and it is estimated that several hundred mAbs are currently in development.

PHARMACOLOGICAL SPECIFICITIES OF MABS

Pharmacokinetic and pharmacodynamic (PK/PD) analyses are essential steps in the early drug development process. Antibody drugs often exhibit PK/PD properties that are much more complex than those typically associated with small-molecule drugs (i.e. organic compounds with molecular weight <1,000 Da).[1]

ABSORPTION

Most of the marketed antibodies are labeled for intravenous (IV) administration, but several mAbs are under development or have been approved for intramuscular (IM) or subcutaneous (SC) injections. The SC route is of growing interest as an administrative method, however, factors affecting the bioavailability, such as catabolic first-pass clearance, SC transport processes and translation of SC animal data to humans, require further research.[6] Oral administration of mAbs for systemic therapy is not indicated, because of their size, polarity and gastrointestinal degradation, which preclude adequate bioavailability.[5]

The bioavailability of mAbs after IM or SC administration varies between 50 and 80%.[3] As a rule, after SC administration mAbs with molecular weight (MW) >16kDa are largely absorbed into the lymphatic system (slow absorption rate), while those <2kDa are absorbed into the blood circulation.[4,5] In summary, after IM or SC injection, absorption proceeds slowly, and the time to reach maximal plasma concentrations (tmax) typically ranges from 2 to 8 days.[2]

There is a relatively new, and growing interest in the development of mAbs for pulmonary delivery, as the lungs have a very large surface area and a high perfusion rate. In addition, pulmonary epithelial cells are known to express neonatal Fc-receptor (FcRn), which may facilitate efficient systemic absorption of antibody delivered to the lung.[13] However, similar to, or even more than, SC and IM administration, the feasibility of pulmonary delivery of mAbs is limited to those with very high dose potency, as only small volumes of fluid can be administered.[1,3]

DISTRIBUTION

Analysis of antibody distribution is much more complicated than the analysis of the distribution of most small molecule drugs. mAbs are often designed to bind with high affinity to tissue sites containing the target antigen; however, because of their large size and hydrophilic nature, they have a slow distribution to peripheral tissue.[3] Unlike small molecules, the paracellular movement of biologics is mainly via convective transport instead of passive diffusion.

Additionally, for macromolecular protein drugs such as mAbs, it is likely that a significant fraction of drug elimination occurs from tissue sites that are not in rapid equilibrium with plasma. In such situations, non-compartmental analysis of plasma data will lead to an underestimation of the distribution volume (Vd). When significant drug elimination occurs from "peripheral compartments", it is not possible to obtain precise estimates of Vd from analysis of plasma data alone. Plasma concentrations may be used to define the range of possible values for the distribution volume, but the determination of tissue concentration by biopsies or imaging technics would provide more insight into distribution.[2]

If the target of the mAb is localized in tissue, slow and/or low distribution to tissue from the systemic circulation may be an obstacle to achieving clinical responses. Alternatively, antibody fragments, consisting of only an antigen-binding part (Fab fragments) or single-chain variable fragments, can cross the blood-tissue barrier more easily and hence are less hindered by this "binding-site barrier" and poor distribution compared to intact mAbs.[3]

ELIMINATION

Because of their molecular size, mAbs are not generally excreted into urine, but are metabolized to peptides and amino acids that can be re-used in the body for the de novo synthesis of proteins, or are excreted by the kidney. A few mAbs with a molecular weight <69 kDa are mainly cleared by renal excretion, and thus the clearance of these biologics can be compromised in patients with renal impairment.[5] Several elimination mechanisms are reported to be involved in mAbs elimination, of which the three most commonly observed are proteolysis by the liver and the reticuloendothelial system (RES), target-mediated elimination, and nonspecific endocytosis.

First, phagocytic cells such as macrophages and monocytes are expected to play a role in the elimination of mAbs, as they are also key factors in the elimination of endogenous IgG. Internalization and subsequent degradation of IgG by lysosomes in these cells occurs predominantly after binding of the Fc part of the antibody to Fc -receptors expressed on these cells.[3]

A second elimination route is degradation of the mAb within the target cell after internalization and subsequent intracellular degradation in its lysosomes. For mAbs targeting an antigen located on cells, degradation by target cells after binding of the Fv-part to the target antigen (target-mediated elimination) is probably the most important elimination route. As this route is saturable as a result of the confined amount of target antigen, non-linear elimination has often been reported for mAbs.[3] The rate of uptake and elimination of antibodies by target-mediated pathways is a function of dose, the expression level of the target, the kinetics of receptor internalization and intracellular catabolism.[1]

Finally, mAbs may also be taken up into cells in different tissues by non-specific pino- or endocytosis. After uptake in the slightly acidic environment of the endosomes in endothelial cells, the immunoglobulins bind to the FcRn. After binding, the IgG-FcRn complex is transported back to the cell surface, where it is released again into the circulation. In contrast, unbound IgG is degraded into amino acids by lysosomes present in the cell[3]. In the absence of target-mediated drug clearance most IgG-based mAbs exhibit long half-lives, typically three or four weeks, mainly as a result of FcRn-mediated antibody recycling.[5]

Another distinction between small molecules and biologics is that biologics can be immunogenic, leading to the formation of neutralizing anti-drug antibodies (ADA). It has been shown that the change in elimination rates resulting from immunogenicity may be either increased or decreased, depending on the number of sites on the therapeutic mAb that the endogenous anti-mAb are directed against. Because of individual differences in the immune response to mAb administration, it is difficult to predict how immune response influences the elimination rate of therapeutic mAbs and whether a change in the elimination rate has clinical implications.[3] The degree of humanization, route of administration, duration of therapy, and dose level can also impact immunogenicity.[5]

DESIGNING FIH STUDIES FOR MABS

Since the 1980s, mAbs are increasingly being incorporated into clinical practice as therapeutic options, particularly in oncology and immunology, and several are still under development. While these targeted therapies are predicted to be highly selective and specific, protein-based drugs such as mAbs can have unpredictable safety profiles. This was demonstrated during a disastrous FIH trial in the UK in 2006. All subjects receiving the first dose of active drug TGN1412, a superagonist mAb against CD28, developed a life-threatening, severe adverse reaction, caused by an uncontrollable cytokine release. The maximum recommended starting dose (MRSD) was, nevertheless, determined by the conventional allometric approach from the no-observed adverse effect level (NOAEL) with a large safety factor of 160, resulting in 0.1 mg/kg. However, when using the receptor theory to re-investigate this dose, it was found that 0.1 mg/kg would elicit greater than 90% receptor occupancy. So, in this situation, not only was the pharmacodynamic effect unacceptably high, producing a cytokine storm, the increased receptor occupancy could also have altered the pharmacokinetics of the antibody by decreasing its clearance, thereby further increasing the peak concentration and prolonging its effect.[7,8]

This tragic incident highlighted the importance of, and difficulties in, selecting the safest MRSD in FIH studies with mAbs. One of the lessons learned from this tragedy is that once receptor occupancy starts to increase, the pharmacodynamic and pharmacokinetic response to further dose escalations becomes non-linear. The TGN1412 incident led to the recommendation that the MRSD should also be calculated based on the minimal anticipated biological effect level (MABEL). It is important to determine in preclinical studies whether target mediated elimination occurs, which should be considered when deriving the MABEL.

MABEL is useful for protein drugs because it defines a dose at which receptor occupancy is low. Per the revised EMA draft guideline of 2016, the FIH doses need to be calculated from both NOAEL and MABEL, and the lowest value is recommended for the clinical trial. For biotherapeutics, such as mAbs, with potential agonistic modes of action on key body systems, no more

than 10% receptor occupancy (RO) is proposed as starting dose in a FIH trial.[11] For mAbs with antagonistic actions, a higher receptor occupancy is needed for a pharmacological effect, and therefore a starting dose inducing higher than 10% occupancy may be acceptable. Importantly, the selected starting dose for a FIH trial, as well as the desirable highest pharmacological active doses, should be justified, considering target saturation by mAbs and systemic PK behavior.

Also, according to the draft EMA guideline published in 2016, specific attention should be paid to the preclinical development program of mAb drugs as a support to FIH studies. Data on the functionality of additional antibody domains in animals should be present, for example, the Fc receptor. The demonstration of pharmacological relevance of the animal model(s) for the mAbs under development is crucial, and may include comparison with humans via tissue cross-reactivity studies using human and animal tissues.

Suh and colleagues published a review article in 2016 covering the results of FIH studies with mAbs from 1990 to 2013, with access to the starting dose estimation.[8] The NOAEL-based approach was still the most commonly used MRSD determination method for FIH studies with mAbs (21.5%). The publication year was sig¬nificantly associated with the choice of MRSD determina¬tion method. The proportion of FIH studies that did not report the MRSD determination method was very high, at more than 50%, in 1990-2007, while the MABEL-based approaches were more frequently used in 2011–2013, with an incidence of more than 30%. The increase in adoption of MABEL for the more recent studies reflects the impact of the TGN1412 incident and the EMA guideline that followed. Although the MABEL-based approach produced an MRSD lower than those derived by the other approaches, the average number of dose escalation steps was similar.

Many mAbs are intended to treat different oncological pathologies, and therefore FIH studies in that indication may have some other particularities. The one-sixth highest non-severely toxic dose (HNSTD) has been introduced as an alternative method in estimating MRSD, not resulting in unacceptable toxicities in FIH and reducing dose escalation steps.[9]

Independent of the safety profiles of mAbs, once the oncological indication is obvious the FIH may be performed in patients rather than in healthy volunteers (HV), as a treatment option in the absence of an effective alternative treatment. Consequently, the challenge to avoid the under-dosing of patients is added to the starting dose estimation and dose escalation determination process.[8,9]

Another challenge when developing a mAb is determining the optimal route of administration. Infusion-related reactions (IRRs) are a common side-effect of antibodies that can lead to interruption and termination of a FIH study. The implementation of prophylactic measurements such as H1- and H2-blockers, steroids, paracetamol and the prolongation of the infusion might help to avoid IRRs. Any implementation of such measures in early phase trials substantially influences the further development of the compound.[10] The best approach would therefore be to foresee a continuous observation of patients during the first hours after the injection of new mAb with a well-established treatment schema in an experienced clinical pharmacology unit.

Another factor that should be taken into account when designing the FIH trial of mAb drugs is the possible delayed PD effect related to duration of target inhibition or target mediated PK profile. Sufficiently long follow-up of subjects should be foreseen to monitor possible delayed adverse reactions. Human terminal elimination half-life predicted by modeling and simulation (M&S) and/or by using physiologically based PK (PBPK) modeling may support the estimation of the duration of long-term follow-up period in trials with mAbs administered as single or multiple doses in early phases.

If we follow the EMA guideline (2007), "Medicinal products are defined as potential high-risk medicinal products when there are concerns that serious adverse reactions in FIH clinical trials may occur". Even if mAbs are in clinical research for more than 30 years, they are often still considered high risk because of uncertainties regarding the mode of action, the nature of the target, and/or the relevance of animal models.

However, this is not always the case, for example when

- the mAb mechanism of action is fully investigated with primary and secondary targets,
- target-mediated elimination is of minor role,
- particularly linear PK/PD is observed,
- a mAb drug is on the market with similar physico-chemical and PK/PD properties,
- advanced M&S is assisting all the steps of preclinical and clinical development.

Regulatory agencies and research ethics committees rightly insist on the use of a 'sentinel' group approach in FIH, particularly in the single dose part, comprising one active-treated and one placebo-treated subject at the start of the study, and at each dose increment. This approach is mandatory in non-standard situations, such as when drugs are first-in-class, if their anticipated physiological effects are potentially profound, and when non-linearity in PK/PD is suspected. This is likely to apply for most mAbs. The intention is to identify any highly repeatable serious adverse event in a single subject rather than being faced with an entire cohort in trouble, as happened in the TGN1412 trial.[12] Which data to analyze from the sentinel group, the time needed to observe them before proceeding, and whether this should be done in every escalation step, are additional challenges that will need to be solved by clinical and PK/PD experts.

CONCLUSION

The pharmacokinetics and pharmacodynamics of mAbs are complex and differ from those of non-mAb drugs. There are numerous PK factors that should be taken into account when designing and running an early phase clinical trial, especially if an antibody has a novel mechanism of action. The growing shift from NOAEL to MABEL, in particular, has the potential to reduce the risks to trial subjects being dosed with a novel mAb for the first time. Careful trial design, informed by knowledge of an antibody's pharmacokinetic peculiarities, is essential if the trial is to run both smoothly and safely.

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