30.06.2021

Translational PK/PD and Model-Informed Drug Development (MIDD) of monoclonal antibodies

Since the first market placement of a monoclonal antibody (mAb) in 1986, more and more treatments from this category of therapeutics have taken their place on the market. At PhinC Development – as a member of MabDesign – we support sponsors throughout their monoclonal antibodies development process.

To introduce monoclonal antibodies and to explain the interests of pharmacometrics in mAbs development, we interviewed Blaise Pasquiers, who is a pharmacometrician at PhinC Development. Blaise is a pharmacist by training specialized in population pharmacokinetics (PopPK) modelling and involved in a research project focused on the modelling of mAbs.

What are monoclonal antibodies?

Antibodies are proteins innate to the immune system. They can recognize an infectious microorganism, such as a virus, a bacteria or cells identified as pathogens. These proteins, or otherwise known as antibodies, can bind to the pathogen and send a signal to the immune system for its' destruction.
Monoclonal antibodies are antibodies that are made by in vitro culture of cells which are than directed to recognize a specific target. Therefore, monoclonal antibodies have the potential ability

to neutralize specific targets, with the help of the immune system, without impacting other proteins or cellular structures. The targets are often selected due to their involvement in a disease, such as a tumour or an inflammatory disease.

What are the stakes of a monoclonal antibodies (mAbs) versus small molecules?

Due to their mechanism of action, mAbs allow a targeted treatment and are often described as the treatments of the future. With that said, mAbs are large molecules (~150 kDa) and this characteristic differentiates their pharmacokinetics (PK) behaviour as opposed to traditional small molecules.
Notably, mAbs aren't absorbed orally (very limited bioavailability: typically, less than 1 or 2%). The preferred route of administrations are SC (subcutaneous) or IV (intra-venous) making the half-life of a mAb a major component during the development of a mAbs. Additionally, due to mAbs' large size, their clearance cannot be hepatic nor renal, and requires a non-specific elimination via phagocytosis and a specific target-mediated drug disposition (TMDD). Generally, the first mechanism is linear, while the second one (TMDD) is saturable. The TMDD elimination is a typical feature of mAbs, and it is usually identifiable on the PK profile at the lowest concentrations of the drug (i.e., when the target is not saturated).

what are the pharmacometrics interests for mAbs?

Pharmacometrics is essential to learn, describe, and predict PK and PD of therapeutics. In preclinical development it is used to predict the safe starting dose in human, to identify the efficacy dose and to evaluate and anticipate the activity of the proposed clinical doses. During clinical development, pharmacometrics enables the description of the therapeutic's PK/PD in term of efficacy and safety of the drug, to identify potential covariates, assess drug interactions with other molecules, and thereby to support dose selection and optimal design.
However, mAbs modelling has many limitations. The relationship between concentration and effect in vivo is poorly understood and PK data are insufficiently used during the dose choice. Better knowledge of mAbs PK is therefore an essential step to optimize the therapeutic use of mAbs.
At PhinC, we are conducting a research project which aims to improve the use of modelling in mAbs development and to develop a MIDD (Model Informed Drug Development) approach for mAbs.

Can you tell us more about this project?

Antibody therapeutics have blossomed into diverse platforms (e.g. bi-specific, multispecific and glycoengineered antibodies) driven by biological insights and engineering technical advances which present new challenges in applying quantitative pharmacology and translational PK/PD. Indeed, anticipating the potential PK non-linearity and associated toxicological effect remain major obstacles. The aim of this research will be to identify innovative modelling methodologies to address this problematic.

Different research questions will be studied as :

- Translational prediction for first-in-human (FIH) dose
- Identify the efficacy dose (dose that reach a sufficient percentage of receptor occupancy)/ Evaluate activity of the proposed clinical doses (PBPK-PD)
- Guide dose escalation in phase I studies and anticipate PK non-linearity
- Improvement of binding to the neonatal Fc receptor (FcRn) as a strategy to extend the in vivo half-life and slow their systemic clearance

And specifically for mAbs bi-specific (BsAbs),

- For every combination of targets, delineate the influence of targets on the PK