NDA Article
Translational Research

Before a drug candidate can transfer from the lab into clinical testing, there must be robust non-clinical data ensuring that it will not expose patients to an unacceptable risk. The evidence available must be sufficient to qualify the translation from in vitro and in vivo models to First-in-human (FIH) studies.

Get the translation right

Early clinical development has an intrinsic element of uncertainty regarding the possible benefits and risks of a novel drug candidate. Risks may derive from the compound's mechanism, the nature of the target and the availability of biomarkers, just to mention a few. This is why the non-clinical data on pharmacodynamics, pharmacokinetics and toxicology and their translation to human are paramount for planning the progress to FIH studies.

The preclinical phase of drug development determines the pharmacodynamic effects, pharmacokinetics, and the safety of the drug. Researchers must examine how the drug behaves to assess safety. Drug metabolism and pharmacokinetics studies, such as ADME (Adsorption, Distribution, Metabolization and Excretion) and toxicology studies, are critical steps in this process.

By careful design of the non-clinical studies and gathering the relevant knowledge in a development programme, this uncertainty can be reduced one step at the time. To identify and mitigate the potential risks to the clinical study several steps can be taken including:

- Ensuring adequate quality of the product
- Conducting additional non-clinical testing if deemed necessary, to obtain relevant data for the risk assessment
- Careful selection of the starting dose, dose escalation and the maximum exposure based on the non-clinical data at hand.
- Applying appropriate risk mitigating measures in the design and conduct of FIH studies.

For advanced therapies, pharmacokinetics is even more challenging. If a conventional drug shows adverse effects, treatment can be halted and after some time, hours to months, the drug has passed the system and is no longer present in the body. CAR T cells are an example of living drugs, and once activated by their receptor they will divide and create a drug response for as long as there are targets.

Immunogenicity

Immune responses to biotherapeutics, including cell-and gene therapies may cause problems for patient safety and product efficacy as they can provoke undesirable reactions. Immunogenicity is difficult to predict in patients, and the potential consequences range from no clinical significance to reduced efficacy of the treatment or hypersensitivity reactions. Therefore, the contribution of early innate and long-term adaptive cellular immune responses leading to anti-drug antibodies (ADA) formation should be taken into consideration in the early stages of product development.

1. Efficacy issues:

Patients treated with biologics frequently develop ADAs which can neutralise the drug and cause treatment failure. The development of ADAs is influenced by a variety of factors, either related to the patient, the treatment, or to the product itself. Although many of the immunogenicity risk factors are understood, immune responses to biologics cannot be predicted based solely on characterization of these factors or in non-clinical models.

2. Safety issues:

The unpredictable adverse reactions of immunogenicity may vary widely and are often unpredictable. It could be acute allergic reactions or infusion reactions. Cytokine release syndrome caused by the rapid release of proinflammatory cytokines from target immune cells. Although not directly related to immunogenicity, the clinical presentation of cytokine release syndrome overlaps with anaphylaxis and other immunologically related adverse reactions. Non-acute reactions, where the association between delayed hypersensitivity and immune responses may be more difficult to establish. Also, cross-Reactivity between ADAs and endogenous proteins which can have severe consequences as it may inhibit vital protein function.

How to pick the right model

In preclinical studies animal models are used as an important step before translation to clinical trials in order to demonstrate that novel therapies are safe and effective. However, there may be differences in biological responses in animals compared to humans. The model should ideally reproduce the full spectrum of aetiology, mechanisms, pathogenesis, and morphology of the human disease in question, something that can be further complicated by the level of molecular complexity in many diseases. The relevance of the animal model includes comparison with humans of target expression, pharmacodynamics, metabolism and other pharmacokinetics aspects.

Animal studies for highly species-specific medicinal products may:

- not reproduce the intended pharmacological effect in humans;
- give rise to misinterpretation of pharmacokinetic and pharmacodynamic results;
- not identify relevant toxic effects.

When it comes to advanced therapies, such as modified T cells, safety pharmacology studies in animal models is ineffective as injecting human cells carrying human receptors will not provide a relevant readout.

Finding the right dose

The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility. This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects.

The clinical starting dose depends on various factors, including pharmacodynamics, particular aspects of the candidate compound, and the proposed design of the clinical trial. Some other important factors to consider when the first-in-human dose is established include: All relevant non-clinical data, including pharmacological dose-response studies, pharmacological/toxicological profile, and pharmacokinetics studies. The No Observed Adverse Effect Level (NOAEL) provides very important information regarding the level of exposure at which there is no significant increase in the frequency or severity of any adverse effects.

The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose. The exposures achieved at the NOAEL in the most relevant (albeit not necessarily the most sensitive) animal species used should be used for estimation of an equivalent human dose.

In contrast, dose-ranging studies in oncology drug development mainly focus on identifying the maximum tolerated dose (MTD) which is primarily based on tolerability and performed in Phase I trials. Changes are coming, though. In a new initiative, the FDA launches Project Optimus, a framework that will assist developers in establishing an optimal biological dose early in development of cancer therapies.

Conclusion

Despite an explosion in new knowledge on the molecular mechanisms of disease, translation into effective treatment for human patients is lagging. Much of pre-clinical research is based on isolated systems and animal models which do not accurately represent the complexity of the human body. At NDA, we can support your translational activities by ensuring that your product is adequately characterized from a safety, mechanistic and quality point of view, and that the evidence you are generating is sufficient to provide a path into human trials.

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