Minireview Article

Determining Maximum Recommended Starting Dose of Systemically Administered Biologics in First in Human Clinical Trials

Abstract

Determining Maximum Recommended Starting Dose (MRSD) in first in human (FIH) studies is a crucial milestone in the development path of a new pharmaceutical drug. It is imperative determine what is the safe starting dose in these trials, as the drug would be introduced for testing in humans for the first time. There are guidelines from United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMEA) that help in determining this dose. Several determination methods for calculating MRSD are in practice, including Minimal Anticipated Biological Effect Level (MABEL), No Observed Adverse Effects Level (NOAEL), Minimum Effective Dose (MED), and Model-based approach. This paper elucidates NOAEL and MABEL methods for calculating the starting dose. This paper also discusses the factors that help in determining which method to choose for a particular study.

Keywords: MABEL; NOAEL; MRDS; maximum recommended starting dose; FIH; First in Human Clinical Trial

Introduction

In first in human (FIH) studies usually the drug is administered in healthy volunteers. [1,2] On some occasions, instead of healthy volunteers, volunteering patients may be included in the study, especially when the drug is known to have unavoidable toxicity, like many cytotoxic agents and biologics.[1,2] Maximum Recommended Starting Dose (MRSD) in first in human (FIH) studies is a crucial determinant needed in the development of a new drug.[2,3] It is not easy to determine what could be the safe starting dose in these FIH trials, as the drug needs to be introduced for testing in humans for the first time. At this point of time (at the time of initiation of FIH study), there are some uncertainties regarding animal toxicity and the mechanism of toxicity.[1] Also, comparability of pharmacokinetics in animals and humans may differ significantly as bioavailability, metabolism of the drug, and toxicity due to a metabolite of the drug (and not the parent drug itself).[1] There are guidelines from United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMEA) that help in determining this dose.[3]

Several determination methods for calculating MRSD are in practice, including Minimal Anticipated Biological Effect Level (MABEL), No Observed Adverse Effects Level (NOAEL), Minimum Effective Dose (MED), and Model-based approach.[3-6]

US FDA guidance on mitigating risks for FIH clinical trials involving healthy adult volunteers

US FDA guidance provides the common conversion factors for deriving a human equivalent dose (HED).[1] It also provides guidance regarding how to derive MRSD from animal data.[1] The relevant data available from preclinical studies, pharmacologically active dose information, toxicology profile, and pharmacokinetics data should be taken into account while deciding MRSD.[1] Lower than the MRSD can be used in FIH clinical trials if so needed to achieve some objectives.1 FDA guidance is based on administered doses to develop an algorithm that helps determine starting dose in humans by extrapolating animal data.[1]

Once toxicology data is available, the first step is to calculate NOAEL (No Observed Adverse Effects Level) for each species.[1-3] NOAEL is defined as "the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group".[1] This dose in mg/kg in the animal species is divided by body surface area conversion factor (BSA-CF) to get mg/kg dose in humans, called human equivalent dose (HED).[1] BSA-CF is a unitless number and converts mg/kg dose in an animal species to mg/kg dose (HED) in humans.[1] Different animal species will generate different HED.[1] The animal species that generates the minimum HED is considered as the most sensitive species for that drug.[1] If no additional information is available to influence the choice of species for assessing risk in humans, then HED derived from NOAEL of this most sensitive species should be chosen for further calculations.[1]

Regardless of which species is most sensitive, an assessment is made, and a species is chosen that could be more appropriate to assess risks in humans.[1] The HED derived from NOAEL of this species is used for further calculations.[1] Many biologics are highly selective for binding to human target proteins.[1] These biologics may have limited binding potential with animal proteins. In such cases before designing toxicology studies, in-vitro studies may be conducted to select an appropriate species that most closely resembles drug behavior in humans (with reference to the protein binding potential).[1] Decision on choosing a most suitable species may also be influenced by factors like whether the parameters of interest can be monitored (for example heart evaluations), and species-specific toxicities.[1] Sometimes, there could occur species specific toxicities, as experience in a particular therapeutic class, based on historical data. Such a species should not be considered for deriving HED.[1]

Once HED is determined, a safety factor of at least 10 should be applied to it, so that the dose is safer.[1] Safety factor should be greater if there are safety concerns observed in animal studies.[1] In this example, we will take safety factor as 10. HED should be divided by this safety factor (10 in this example) to get MRSD. Why safety factor should be applied? This is because not all symptoms may have been possibly monitored in animal studies.[1] Example, visual disturbances, headache- these symptoms may not have been possible to be monitored in animal studies and may become dose limiting for humans.[1] Also, pharmacokinetics may differ in animals and humans.[1]

The process of calculating MRSD by the NOAEL method has been described in detail in the FDA guideline (see reference).[1]

European Medicines Agency's guidance on mitigating risks for FIH clinical trials

European Medicines Agency (EMEA or EMA) guidance recommends calculation of MRSD based on NOAEL. EMEA also recommends calculating MABEL (minimal anticipated biological effect level), and PAD (physiologically active dose).[2] MABEL calculation is based on pharmacokinetics, pharmacodynamics data, sensitivity differences in mode of action of the drug between humans and animals, and target binding.

Besides calculating MABEL in humans, pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans can also be calculated.[2] The starting dose in healthy volunteers should generally be a dose that would cause lesser exposure than physiologically active dose (PAD).[2] The starting dose should be related to either of the three, MABEL, PAD or NOAEL. Safety factors are generally applied to further decrease the risk of adverse events.[2]

Methods of Determining MRSD

The two commonly used approaches for calculating MRSD in biologics FIH trials are given below:

- **No Observed Adverse Effects Level (NOAEL):** This is the most used method to determine MRSD of monoclonal antibodies for FIH studies and has been described above. [1-3,7] This approach is based on the concept of development of adverse events.[1,3,8]
- **Minimal anticipated biological effect level (MABEL):** This approach is increasingly becoming popular since 2011.[3,8] Rather than depending on development of adverse events, this approach focusses on anticipated biological effects.[8] Since many biologics, even at low doses, can cause serious adverse events including cytokine release syndrome and neurotoxicity, MABEL approach based on anticipated biological effects rather than adverse events, is gaining popularity in determining starting dose in FIH clinical trials.[6,8] This approach was first introduced by EMEA in 2007, and later gained acceptance by FDA, and is increasingly being used in both EU and USA FIH clinical trials.[8] MABEL approach utilizes detailed in vitro and in vivo pharmacokinetics and pharmacodynamics data, including target binding and receptor occupancy (including in vitro in target cells from both human and animal species), and anticipated exposure.[4,6-8] Additionally, a safety factor is applied for further reduce the risks.[2] As there are several adjustments done using this approach, including adjustments based on anticipated exposure in humans, anticipated duration of effect, and inter-species differences in potency of the drug and its affinity to the receptors, this is rapidly becoming a favored approach to calculate the starting dose for FIH clinical trials.[5,6]

Conclusion

Determining maximum recommended starting dose based on pre-clinical data is a critical step in FIH clinical trials.[1-3] US-FDA and EMEA have published guidelines that help in determining the MRSD.[1-3] NOAEL approach is most used to calculate MRSD, and is described in detail in US FDA guidance.[1] MABEL approach is dependent on pharmacology data collected in preclinical studies for calculating MRSD, and is rapidly becoming popular, especially in clinical trials involving biologics. This is because even at low doses many biologics can cause serious adverse events including cytokine storm and neurotoxicity, making it important to base starting dose calculations on methods that use pharmacokinetics and pharmacodynamics (like MABEL) and not just adverse events (like NOAEL).[6-8] In both approaches (NOAEL and MABEL) a safety factor is used to further decrease the risk of adverse effects, adding to safety of subjects in FIH trials.[2]

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we

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