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

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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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 to 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), and Minimum Effective Dose (MED) 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.

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1. 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) may differ in humans and animals [1]. This is especially true of humanized monoclonal antibodies that are specific for humans. There are guidelines from United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMEA) that help in determining this dose [3]. Due to the tragedy of TGN1412 clinical trial, in which all 6 healthy volunteers had cytokine storm and multiorgan failure (though all survived with aggressive management), there has been a lot of caution on selecting a safe dose for first in human (FIH) and first in patient (FIP) studies. Triggered by this tragedy, MABEL (minimum anticipated biological effect level) approach was recommended by EMEA in 2007, and later was adopted by US-FDA [1].

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) approach, and modelling and simulation approach [3-6].

2. 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]. FDA recommends that 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]. Dose 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 and on the 'No Observed Adverse Effect Level (NOAEL)' 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), a unitless number, to get mg/kg dose in humans, called human equivalent dose (HED) [1]. Different animal species generate different HED [1]. The animal species that generates the minimum HED is considered as the most sensitive species for that particular drug [1]. HED derived from NOAEL of this most sensitive species should be chosen for further calculations of MRSD if no additional information is available to influence the choice of species for assessing risk in humans [1]. An attempt is made to choose a species 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, but they may have limited binding potential with animal proteins [1]. 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 monitoring of the heart), and species-specific toxicities [1]. If there are there species specific toxicities (as seen in historical data of a particular therapeutic class), 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 in humans [1]. Safety factor should be greater than 10 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]. For example, visual disturbances, headache- these symptoms may not have been possible to be monitored in animal studies and if they occur in humans, they may become dose limiting [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].

3. 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 approach is favored while calculating starting dose of biologics or cytotoxic drugs, as even at lower doses these drugs can cause serious adverse events. 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].

4. 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 and has been described above [1-3,7]. This approach is based on the concept of development of adverse events [1,3,8]. But, in clinical trials involving biologics or cytotoxic drugs, MABEL approach (described below) has become very popular [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 [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, to further reduce the risks to humans, a safety factor is applied [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 approach has become very popular to calculate the starting dose for FIH clinical trials [5,6].

5. FIRST IN HUMAN (FIH) AND FIRST IN PATIENT (FIP) CLINICAL TRIALS IN ONCOLOGY BIOLOGICS

Method of starting dose calculation of biologics in oncology FIH/FIP clinical trials differs based on mode of action of the drug, and its pharmacological properties [9]. MABEL approach is commonly used for biologics that have an agonistic action [9,10]. If non-immune activating biologics are involved, then typically NOAEL approach is used to calculate MRSD [9]. In 2006, Ganesh Suntharalingam, et al reported incidence of cytokine storm in all 6 healthy young male adult volunteers who were administered TGN1412, an anti CD-28 monoclonal antibody that is a direct stimulant of T cells in a FIH clinical trial [11]. All these 6 healthy volunteers developed systemic inflammatory response due to release of proinflammatory cytokines within 1 ½ hours of receiving a single intravenous dose of

the monoclonal antibody [11]. Within 16-18 hours of the infusion, the inflammatory response progressed, and all 6 became critically ill, with multiorgan failure, and disseminated intravascular coagulation [11]. These were aggressively managed, and all these 6 volunteers survived [11]. This incident led to cautionary approach to selection of the starting dose [9,12]. Next year, in 2007, EMEA proposed MABEL approach to calculate MRSD for products that are likely to activate immune system [9]. Since then, MABEL approach has become increasingly popular, choosing a starting dose that results in no more than 10% of receptor occupancy [5-6,9,10,13,14].

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].

DISCLAIMER

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 do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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