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Practical approaches to dose selection for first-in-human clinical trials with novel biopharmaceuticals ☆

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ABSTRACT

Recent advances in our understanding of disease biology, biomarkers, new therapeutic targets, and innovative modalities have each fueled a dramatic expansion in the development of novel human therapeutics. Many are biotechnology-derived biologics possessing high selectivity and affinity for their intended target; as such they often pose challenges in the development path to approval. One challenge is the selection of the first-in-human (FIH) dose. This process has come under increased scrutiny as a result of a FIH trial with a super-agonist monoclonal antibody (TGN1412), which resulted in significant injury to healthy volunteers. Regulatory agencies have responded with supplemental guidance for the development of novel therapeutics. The intent of this paper is to provide experience-based insight, with relevant examples, for those planning the first administration of novel biopharmaceuticals in humans.

1. Introduction

A rapid expansion of novel technologies for developing new medicines has occurred over the past 20 years. This expansion has been driven by the discovery of new targets and improved knowledge of cellular mechanisms and pathophysiology. As a result, novel biopharmaceuticals (also referred to as biotechnology-derived pharmaceuticals, biotherapeutics, or biological drugs) can now be developed with high degrees of selectivity for specific targets. Nevertheless, uncertainty remains regarding many cellular pathways and the concordance of physiology and pathology between humans and animals. Increasing innovation has resulted in expanded diversity in therapeutic modalities including novel chemokines, armed antibodies, and oligonucleotide-based therapies; each of these has its own uncertainties which may lead to a higher risk of unintentional, unrecognized, or poorly understood effects in humans.

The events related to the FIH study of TGN1412 (TeGenero AG, Würzburg Germany) provide a rare but vivid example of the limitations in extrapolating animal data to humans (Expert Scientific Group, 2006; Suntharalingam et al., 2006). Healthy subjects who received a super-agonist antibody against the T-cell target, CD28,

Abbreviations: ADA, anti-drug antibodies; AUC, area under the time vs. concentration curve; BSA, body surface area; EMA, European medicines agency; FIH, first-in-human; HNSTD, highest non-severely toxic dose; HED, human equivalent dose; MABEL, minimum anticipated biologic effect level; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PAD, pharmacologically active dose; PD, pharmacodynamics; PK, pharmacokinetics; STD_{10}, dose severely toxic to 10% of animals; HNSTD, highest non-severely toxic dose; LOAEL, lowest observed adverse effect level.

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experienced an unanticipated "cytokine storm" which necessitated intensive care and resulted in prolonged morbidity in some volunteers (Suntharalingam et al., 2006). While this example emphasizes the need for caution, it is important to understand that FIH studies have in general been remarkably safe for the thousands of biopharmaceuticals introduced into the clinic (Colburn, 1990; Sibille et al., 2006).

Preclinical data must support a level of risk considered acceptable for a new therapeutic to be given to humans for the first time. There is no medical benefit to healthy subjects or those with disease in the initial clinical trials. Therefore, to optimize safety in a FIH trial a comprehensive understanding of the molecule, its target, and expected behavior in both diseased and normal tissues is needed. This is especially important for biopharmaceuticals with slow elimination such as monoclonal antibodies, where the potential for persistent target modulation and alteration of downstream cellular processes require careful assessment.

In response to the 2007 TeGenero event, the EMA, through its Committee For Medicinal Products for Human Use, issued a "Guideline on Strategies to Identify and Mitigate Risks for First-In Human Clinical Trials With Investigational Medicinal Products" (EMEA, 2007), a document aimed at helping developers identify and mitigate the risks associated with FIH trials. This document complements the 2005 Food and Drug Administration Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (FDA, 2005). These guidance documents, together with the ICH Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH, 1997), provide important information to investigators and developers involved in the design and interpretation of preclinical programs supporting FIH trials. An addendum to this Guidance, ICH S6(R1) is at this time under review. This addendum may provide additional guidance to developers preparing for FIH trials, particularly in the areas of species selection and preclinical study design (ICH, 2009). While these documents are valuable resources for developers planning FIH studies with novel biopharmaceuticals, it is useful to also review experiences and lessons learned in implementation of the guidance documents. Herein, our aim is to provide an overview of best practices for those planning first administration to humans.

2. The building blocks of a FIH dose

2.1. Overview

Selecting a FIH dose requires the integration of data from many disciplines. From careful experimentation, one gathers a thorough understanding of the behavior of the new therapeutic including: mode of action, receptor interaction, duration of effect, reversibility, kinetics, potential for off-target pharmacologic effects or species-specific activity, preclinical PK, and toxicologic potential (Fig. 1). Once sufficient preclinical data are available, a dose is then selected, guided by a relevant endpoint (e.g., NOAEL, MABEL, or PAD) to determine the human equivalent dose (HED). A final step in extrapolating an initial safe starting dose is to apply a safety factor, which takes into consideration the overall robustness and quality of the data, as well as the potential for adverse effects in the intended FIH population. This approach is fundamentally the same whether the target is soluble or cell-based, or is expressed only in disease states. The following discussion highlights the key steps in selecting an FIH dose by emphasizing points to consider and providing useful examples.

2.2. Preclinical models of toxicity

The cornerstone for estimating a FIH dose is, as far as possible, ensuring the relevance of the in vitro or ex vivo test systems and in vivo animal models to humans (Fig. 1). Ideally an "appropriate" or "relevant" species or model for evaluation of toxicity (Cavagnaro, 2002; FDA, 2005; ICH, 1997), exhibits the following characteristics:

(a) The therapeutic target is expressed in that species with a similar tissue distribution to humans;
(b) Similarity in the interaction of the therapeutic agent and its target in the preclinical species and humans, specifically:
    i. target homology;
    ii. epitope for monoclonal antibodies;
    iii. binding affinity and kinetics;
    iv. similar dose and concentration dependence of pharmacologic response;
(c) The downstream pharmacologic effects in the preclinical species reasonably mimic those expected in humans.

The choice of appropriate animal models is justified by gathering sufficient data supporting the criteria listed above and is made in collaboration with discovery scientists familiar with the product and its target. That body of data might include: in vitro binding affinity data in humans and each preclinical species, kinetic data, comparative in vitro or ex vivo studies of the concentration–response relationship, and in vivo PD evaluations such as comparison of the change in circulating B-cell populations in primates and rodents following treatment with an antibody to a B-cell target.

For preclinical studies to be relevant they must be conducted in an appropriate species. Sometimes this is possible and sometimes it is not. For example, mice are an appropriate species for evaluating the function of CD20 in humans (Uchida et al., 2004). In both species, CD20 expression is primarily restricted to B-cell lineage and mediates Ca^{2+} transmembrane migration, and B-cell tissue also shares humoral immune response function in each species. Thus, demonstrating similar binding of the therapeutic to the species-specific CD20s is sufficient to establish the mouse as a relevant model for assessing human safety. In contrast, interleukin 5 (IL5) is a T-cell derived cytokine that does not share identical functions in humans and mice (McKenzie et al., 1991). While the cytokine induces eosinophil production and activation in both species, IL5 has additional activity on B-cells in mice. In this case, even though the interaction of IL5 with its receptor may be similar between mice and humans, differences in downstream activity make the mouse of more limited relevance for assessing human safety. Another example of an inappropriate test species would be the use of dogs as the non-rodent species for toxicologic assessment of human TNF-α (Ferrari, 1998). Dogs are hyporesponsive to this cytokine in comparison to humans, potentially leading one to overlook or minimize the cardiovascular effects of TNF-α.

Developers may be faced with situations where an appropriate preclinical species is not available. In such cases, studies with alternative systems (e.g., homologous proteins or transgenic animals expressing the human target) may provide a strategy that better defines an "appropriate" species. However, the use of such systems may still have limitations with respect to extrapolation to humans. In complex biologic systems, such as the immune system, even though the target can be pharmacologically manipulated, the physiological consequences may be importantly different from humans (Horvath and Milton, 2009; Muller and Brennan, 2009; Suntharalingam et al., 2006). Careful examination of the alternative system should be undertaken to identify strengths and limitations in order to justify its suitability to assess toxicity (Bussiere et al., 2009).

Determining the FIH dose based on in vivo data from animals is not an exact science. A thorough understanding of the predictive value of the model coupled with complementary in vitro and ex vivo studies will improve the assessment of risk and should lead to a rational strategy for risk mitigation. The choice and availability of an appropriate preclinical species for assessment of toxicity is a critical