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Meeting report

Preclinical safety testing for cell-based products using animals

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ABSTRACT

The objectives of preclinical testing include to show why there might be therapeutic benefit in patients and to provide information on the product's toxicity. For cell-based products, given even once, there may be long term exposure and this could imply, unlike for conventional drugs, that all preclinical studies may be needed prior to first human use. The duration of exposure to cells should be studied in animals to guide toxicity assessments. Distribution of cells after administration by a route resembling that intended in humans should be studied to understand potential risks. Risk of tumour formation with the product may also need to be characterised. To the extent that this information can be generated by in vitro testing, studies in animals may not be needed and limitations on the capability of preclinical data to predict human toxicity are recognised: species-specificity make some cell products act only in humans and a human cell-product might be expected to be rejected by immunocompetent animals. Does this suggest testing in immunosuppressed animals or of development of an animal-cell product supposedly similar to the human cell product? No single answer seems to fit every situation.

1. Introduction

This article is the second of two reflecting two talks given by the author at a meeting[1] in Kyoto, Japan in March 2014. The first addressed the European regulatory framework for the regulation of cell therapies: this article addresses issues relating to preclinical testing to support development of such products, with a particular focus on in vivo studies in animals. The theme of the meeting was to share experience from different territories in the international regulation of such products. In particular, the meeting aimed at discussing how to ensure development of good quality, safe and effective cell therapy products throughout the world.

This article discusses use of animals in preclinical testing of human cell-based therapies. In the development of any type of medicinal product, containing a novel active agent, preclinical testing is conducted in order to provide evidence for expectation of therapeutic benefit in patients, to provide information on what toxicity the drug might possess and to indicate doses for each such effect: it also aims to identify agents which should not be given to humans at all, either because of their inherent toxicity which can translate into a lack of any evident safety margin, or perhaps because the agent in question has unsuitable kinetics; preclinical testing also aims to provide further information to aid understanding of an effect recognised but poorly delineated, whether toxic or beneficial. Limitations of testing in animals are acknowledged [1] and where in vivo studies are not useful or may well be potentially misleading, their omission is justified.

This article addresses:

- aims of preclinical testing
- contrasts between studies for a small chemical drug or a cell therapy product
- regulators' expectations for preclinical data for cell therapy products
- circumstances where an absence of any in vivo testing is appropriate.

2. Compare and contrast: data supporting a first human trial with a novel agent that is a small chemical drug as compared to a cell therapy product

By the time of the first clinical trial, a typical preclinical dataset for a novel small molecule chemical drug will likely include the following:

Abbreviations: ADME, Absorption, distribution, metabolism & excretion; MHRA, Medicines & Healthcare products Regulatory Agency; WHO, World Health Organization.

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[1] Challenges towards sound scientific regulation of cell therapy products, March 7–8th, Kyoto International Conference Center, Kyoto Japan.

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- primary pharmacology – in vitro and in vivo studies supporting the intended therapeutic action;
- secondary pharmacology – in vitro studies into inherent properties of the drug, but which are not the basis of its intended therapeutic effect;
- safety pharmacology – effects on the vital systems, cardiovascular, central nervous and respiratory systems – with interest on effects at likely maximal intended clinical doses;
- pharmaco- & toxicokinetics – exposure, absorption, distribution, metabolism and excretion;
- general toxicity and local tolerability – nature, dose/exposure associated with effects, and reversibility
- genotoxicity – mutagenicity, clastogenicity and in vivo genotoxicity.

This set of data will typically support relatively short term clinical studies into the safety of the product in healthy humans which may also, perhaps, provide clinical data on either pharmacodynamic effects relevant to the intended therapeutic effect, or otherwise give some indication of the potential for efficacy with testing in patients.

For later clinical development, in patients with less close monitoring than applied in early clinical studies, data from reproductive toxicity studies (fertility, embryofetal development and prenatal and postnatal development) and from other toxicity studies (eg phototoxicity, immunotoxicity, dependence, longer term general toxicity studies, metabolite toxicity studies) might be expected. Carcinogenicity studies may be required usually by the time an application for approval to market the product is to be made. These expectations are set out in regulatory guidance [2].

Whereas many small molecule drugs and some non-cell therapy biological products might fit well into this set of studies, to begin the development of a cell therapy product by intending to implement this plan, making modifications as necessary for a cell therapy product, is an inadvisable approach. Rather, a fresh approach should be adopted, based on defining what questions preclinical testing needs to address prior to clinical testing and focussing only on studies that will enable only clinical testing that is both reasonable and safe.

2.1. Primary pharmacodynamics

One key question to answer in preclinical development of a cell therapy product is what evidence suggests there is a reasonable expectation of benefit? Some of the type of primary pharmacology data generated for small molecules is usually not relevant here: there is no parallel with the type of information describing drug-receptor or whether the drug is an agonist, partial agonist, antagonist or inverse agonist – cells of a cell therapy product likely secrete multiple molecules covering all these actions. Nevertheless, evidence supporting use of the cell therapy product must be provided. In some instances, this can be from use cell products in animals with spontaneous disease, rather than from experimentally-induced pathological states in experimental animals. Instances where such data are used are rare: usually, proof of concept data are provided from studies that characterise disease and its cause in humans and from effects noted in experiments in animals that recapitulate some of these features: it may even include specific explorations into the understanding of where experimental system in animals or veterinary pathology differs from that in humans, either for anatomical or pathological reasons. It is also relevant to note and contrast the typically chronic nature of human disease, compared to the usually acute nature of an induced change in experimental studies in animals.

For chemical drugs, defining the dose expected for clinical therapeutic benefit in human patients is based on testing with that molecule. Data on drugs of similar chemical and pharmacological classes can be applied to set proposed human dosing in context, but cannot substitute for data generated with that specific drug in preclinical development. In contrast, with cell therapies, clinical data with similar products are of greater relevance than testing in animals, whether for dose selection or for safety considerations. However, such an approach raises the question of how similar is the product to be used in the proposed trial with that used in clinical studies, results from which are the basis of the dose selection and the claim for the expectation of safety. Where it is feasible to adopt this approach of crossreference to clinical data with products that are claimed to be similar, this is encouraged. The nature of clinical data can also be variable – where a dedicated clinical study with a defined product has been done, it can easily be recognised that this type of systematic data is of greater use in providing a basis to make a decision going forward, than are anecdotal data, perhaps from a case series of patients that have been treated with product that may either be known to have been produced by variable means or the provenance of which is even more uncertain.

Clinical testing with cell therapy products will almost certainly always start with testing in patients with the condition for which the product is being developed; it is almost impossible to imagine use of such products in healthy subjects. This has the consequence that it is probably not reasonable to use doses that are expected to be inactive. The clinical starting dose should therefore be in the range that may be expected to have therapeutic activity and for safety reasons, should likely be positioned at the lowest end of the range of doses that are considered active. Where the product is unlike any for which there is previous clinical experience and/or there are major difficulties in projecting a clinical dose based on studies in animals, then the ability to identify a potentially active dose may be compromised and, there being very little evidence to support higher doses, safety should be the prime consideration driving dose selection, even if this has the consequence that patients in initial cohorts are later recognised to have received an inactive dose. Thus, in contrast to small molecule drugs, where clinical testing is escalated from an initial dose expected to be safe as it has no activity into an anticipated therapeutic range, testing with cell therapy products should first characterise what is expected to be an active dose and then seek to demonstrate why this is expected to be safe: this shows the different mindset appropriate to such products.

2.2. Secondary and safety pharmacology

Potential for unintended effects and for risks of adverse effects on function of vital systems (central nervous, cardiovascular and respiratory systems) should be understood, but for cell products, separate studies are rarely justified and should not be done unless there is a specific consideration that requires this testing. It is likely that general toxicity testing will suffice. In contrast, most small molecules should have some dedicated testing for potential effects on these systems, and perhaps also gastrointestinal and renal system functions [3].

2.3. Kinetics – distribution and persistence

For small molecules, there is interest in understanding and characterising the exposure and elimination of a small molecule drug. This has led to a set of studies that address its absorption, distribution, metabolism and excretion (ADME) with results from animals applied to model reasonable expectations in humans. Toxicokinetic investigations provide data on exposure with

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