First-in-Human Trials of Cellular Therapies

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CIRM / Regenerative Medicine Consortium Roundtable
October 16, 2012

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Overview

- Clinical risks of cellular therapies
- Considerations for clinical protocol design for first-in-human studies of cellular therapies

Risks of Cellular Therapies

- Foremost concern in first-in-human (FIH) trial is safety
- Important to understand the risks so that the trial can be designed to minimize the risks to subjects
- There are special risks with cellular therapies

Potential Risks of Cellular Therapies

- Novelty of products
- Novel and invasive administration procedures often required to deliver the cellular therapy to the intended site
  - Associated procedural risks
- Cells might persist for an extended period or produce a sustained effect
  - Could increase or prolong adverse reactions

Potential Risks of Cellular Therapies

- Mode of action is often not clear, so it may be difficult to predict adverse effects
- Differentiation in vivo into undesired cell types
- Tissues might form ectopically
- Cells might develop undesired autonomous function (e.g., generating electrical abnormalities in the heart)

Potential Risks of Cellular Therapies

- Cells might undergo transformation and form tumors
- If cellular product is manufactured from an allogeneic donor, then there may be induction of immune response to cells
- If cellular product has lymphoid component, it might induce graft-vs-host disease

Risk Information from Animal Studies

- Preclinical studies investigate the safety of an investigational product in animals prior to administration to humans
- Findings may help to
  - Estimate a starting dose that has an acceptable level of risk
  - Estimate duration of product activity in vivo
  - Provide support for a dosing regimen
  - Identify safety issues to be considered in the clinical trial treatment plan or monitoring plan

Risk Information from Animal Studies

- In some instances, although the cellular therapy might appear to be relatively safe in animals, this is not reflected in the safety profile following dosing in humans
  - Possibly due to species specificity of the cell product; for example, the animal may have an immune response to the human cells, resulting in cell rejection or accelerated clearance.

Risk Information from Animal Studies

- In such situations, other scientific data, such as published scientific literature and any human experience with related products, may contribute to decisions regarding starting dose and monitoring plans for a first-in-human trial

"Proof-of-concept" Preclinical Studies

- **Proof-of-concept (aka, proof-of-principle) studies**
  - **No formal regulatory definition**
    - **Studies that provide evidence that a product has a specific activity, or has characteristics that may be necessary to produce a specific effect**
    - **"Product" may include not only the cellular product, but also the delivery device**
  - **Can be in vivo and/or in vitro**

"Proof-of-concept" Preclinical Studies

- Proof-of-concept studies for cellular therapies may provide evidence that
  - Cells reach target location(s)
  - Cells survive long enough to achieve proposed effect
  - Cells have activity on a surrogate that is expected to correlate with a benefit in humans; for example, clearance of amyloid in the mouse brain, for a product being developed for the treatment of Alzheimer's disease

“Proof-of-concept” Preclinical Studies

- Cells have the activity in animals that is targeted as the benefit in humans; for example, prolonged survival in an animal model of ALS

"Proof-of-concept" Preclinical Studies

- Purpose of such studies is to provide evidence of "prospect of benefit" or "therapeutic potential" of the product
  - To justify risks in humans
  - To support sponsor's "go / no-go decisions" regarding further development
- Misnomer: such studies can provide evidence to support further development, but do not "prove" anything regarding efficacy (or safety) in humans

Overview

- Clinical risks of cellular therapies
- **Considerations for clinical protocol design**

First-in-human Protocol Safety Objectives

- Primary objective is an evaluation of safety
  - Identification of safety issues that
    - Might not have been anticipated
    - Were not expected for the doses being administered

First-in-human Protocol Secondary Objectives

- Preliminary assessments of product activity, using either short-term responses or longer-term outcomes
  - Cell engraftment
  - Changes in immune function
  - Physiologic responses
  - Prospective biomarkers

First-in-human Protocol Secondary Objectives

- Evaluation of the feasibility of manufacturing the product in the context of clinical use
- Evaluation of the logistics of a complex administration procedure
- Data addressing secondary objectives could be important for
  - Designing later-phase trials
  - Supporting acceptability of continued clinical investigations for relatively high-risk products

Choice of Study Population

- FDA considers the overall risks vs. benefits for the study population
- Healthy normal volunteers are generally not included in trials for cellular therapy products
  - Products might have long-term risks or permanent adverse effects

Choice of Study Population

- **Subjects with advanced disease and limited treatment options**
  - **Might be preferred population, if their clinical situation makes the risks acceptable in face of uncertain benefit**
  - **Are not necessarily the preferred choice for use in FIH trials for every product and indication**
  - **Might be more vulnerable to adverse reactions, which might increase the risks**
  - **Confounding adverse events due to underlying disease could make safety data difficult to interpret**

Choice of Study Population

- Pediatric subjects present special challenges
  - FIH trials are usually conducted in adults
- Choice of subjects depends on expected risks and benefits, recognizing uncertainty about these expectations in FIH trial
- The objective is to select a study population with an acceptable balance between anticipated risks and benefits

Control Group

- If there is limited experience with the disease or population
  - Expected outcomes for the population might not be available in literature; in such cases, trial safety data from a single-arm study might be hard to interpret; a control group might be useful for comparison
- Can also provide a comparator for preliminary assessments of activity or efficacy

Control Group - Blinding

- **Blinding is usually desirable, but only if it can be done simply and with minimal risk to control subjects**
- **High-risk, invasive procedures for purposes of blinding often present unacceptable risks for a control group in a first-in-human trial**

Starting Dose Determination

- If animal or in vitro data are available, there might be sufficient information to determine if the proposed dose has an acceptable level of risk
- If there are insufficient animal or in vitro data, then clinical experience with related products might justify the starting dose

What Attributes Quantify the Dose?

- Products can be very heterogeneous regarding active and inactive fractions
- Determination of what attribute actually represents the “dose” might be a complicated issue

What Attributes Quantify the Dose of a Cellular Therapy?

- Dosing to target a therapeutic effect might be based on one cell type
- Adverse reactions might depend more on a different cell type in the same product
- Often, the active cell subset is not known, so the dose is based on the total number of cells
  - Collecting data on various cell subsets, with a comparison of clinical outcomes, may identify important cell subsets

Treatment Plan

- **Most FIH trials of cellular therapies include staggered administration to limit overall risk**
- **Staggered administration**
  - **There is a specified follow-up interval between administration to the first subject and administration to the second subject**
  - **The interval is intended to be long enough to monitor for acute and subacute adverse events**

Treatment Plan

- **Staggered administration**
  - **First several subjects in the study might also be staggered in this way**
  - **Trials with sequential cohorts with dose escalation usually include a staggering interval between cohorts**
  - **In some cases, staggered administration within each higher-dose cohort might be appropriate**
  - **Choice of the staggering interval duration depends on the time course of adverse findings in the animal studies, clinical experience with related products, and duration of exposure**

Stopping Rules

- Most FIH trials include stopping rules
- Purpose is to control the number of subjects put at risk, in the event that early experience uncovers important safety problems
- Stopping rules specify a number or frequency of deaths or other serious adverse events that will result in temporary suspension of enrollment and dosing until the situation can be assessed

Stopping Rules

- Based on that assessment, the protocol might be revised to improve safety
- Revisions could include
  - Revising the eligibility criteria
  - Dose reduction
  - Changes in administration procedure
  - Changes in the monitoring plan
- Stopping rules are not intended to terminate a study

Safety Evaluation

- **Duration of monitoring for adverse events**
  - **Sufficient to cover the expected duration of effect**
  - **Duration of monitoring will depend on results of animal studies, experience with related products, knowledge of the disease process, and basic scientific information**
  - **For some therapies, the duration might be indefinite – in that case, protocol typically includes a plan for additional long-term follow-up**

Safety Evaluation

- **Additional long-term follow-up might be appropriate for some cellular therapies, particularly if the cells might transform, migrate, or have the potential to develop ectopic tissue**

Long-Term Safety Monitoring

- Long-term monitoring focuses on
  - Survival
  - Serious adverse events that are
    - Hematologic
    - Immunologic
    - Neurologic
    - Oncologic
- In some situations, a telephone call to the subject, rather than a clinic visit, may be sufficient to obtain necessary follow-up information

“Proof-of-concept” in FIH studies

- **Proof-of-concept (aka, proof-of-principle)**
  - **No strict regulatory definition**
    - **Evidence that a product has a specific activity, or has characteristics that may be necessary to produce a specific effect**
    - **“Product” may include not only the cellular product, but also consider the delivery device**

“Proof-of-concept” in FIH studies

- **Proof-of-concept for cellular therapies may be evidence that**
  - **Cells reach target location(s)**
  - **Cells survive long enough to achieve proposed effect**
  - **Cells have effect on a surrogate that is expected to predict a clinical benefit, or an effect on a clinically meaningful outcome**

“Proof-of-concept” in FIH studies

- Such FIH studies may provide evidence of “prospect of benefit” or “therapeutic potential” of the product
  - Justify risks in humans
  - Support sponsor’s “go / no-go decisions” regarding further development

“Proof-of-concept” in FIH studies

- **FDA recognizes that FIH studies are designed to provide a preliminary assessment of safety, and have limited ability to provide proof-of-concept of efficacy.**

Conclusions

The special characteristics of cellular therapies, and the procedures that might be needed for their administration, present issues for the design of FIH clinical trials that are different from the issues usually encountered with small molecule therapies.

Conclusions

No one design will be applicable for all FIH trials. The design must consider the specific product, the available data, and the proposed indication.

Conclusions

Sponsors of new cellular therapies are encouraged to interact early with OCTGT staff to ensure that proposed FIH clinical trials are designed appropriately for the specific product and clinical indication.

Guidances
Cellular Therapies

- Considerations for Allogeneic Pancreatic Islet Cell Products (2009)
- Cellular Therapy for Cardiac Disease (2010)
- Clinical Considerations for Therapeutic Cancer Vaccines (2011)
- Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (2011)

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Acknowledgements

John Hyde, PhD, MD

Mercedes Serabian, MS, DABT

Acknowledgements

Pharmacology / Toxicology Branch	General Medicine Branch	Oncology Branch
Mercedes Serabian**, MS	Ilan Irony**, MD	Ke Liu**, MD, PhD
Pakwai Au, PhD	Changting Haudenschild*, MD	Peter Bross*, MD
Alex Bailey, PhD	Bruce Schneider*, MD	Bindu George*, MD
Theresa Chen, PhD	Mark Borigini, MD	Chaohong Fan, MD, PhD
Shamsul Hoque, PhD	John Hyde, PhD, MD	Sadhana Kaul, MD
Ying Huang, PhD	Agnes Lim, MD	Robert Le, MD, PhD
Wei Liang, PhD	Steve Winitsky, MD	Lydia Martynec, MD
Jinhua Lu, PhD	Rachel Witten, MD	David Maybee, MD
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