FDA's Biological Response Advisory Committee October 10, 2002

Summary

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Division of Cellular and Gene Therapies, Office of Cellular, Tissues, and Gene Therapies

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GUEST EXPERTS

- Barbara Ballard
- Rebecca Buckley, M.D.
- Crystal Mackall, M.D.
- Stuart Orkin
- Linda Wolff, Ph.D.

Scientific Presentations to the Committee

- Drs. Cristof von Kalle and Alain Fischer
  - X-SCID gene therapy clinical trial in France
  - Scientific data pertinent to the child with monoclonal T cell expansion
- Dr. Rebecca Buckley
  - Current therapeutic options for treatment of SCID (X-SCID, ADA-SCID, and others)
- Dr. Linda Wolff
  - Current data regarding retroviruses and insertional mutagenesis leading to cancer

Scientific Presentations, Continued

- Dr. Christopher Baum
  - Report on study in mice treated with retroviral vector transduced hematopoeitic stem cells
  - Myelogenous leukemia development in this model; proposed mechanisms
- Dr. Stuart Orkin
  - LMO-2 – what's known about the role of LMO-2 dysregulation in human cancer

Presentations from Clinical Investigators

- Dr. Donald Kohn
  - Results from three clinical trials in SCID
    - ADA-SCID (two trials)
    - X-SCID (Weinberg)
- Drs. Brian Sorrentino and Brian Cunningham
  - Results from single-patient emergency IND
    - Child with Jak-3 deficiency
- Dr. Harry Malech
  - Proposed study in X-SCID patients who have had allogeneic transplants, but immune defects persist

Are there additional data or measures that clinical investigators need to provide before future and present clinical trials in SCID patients should proceed in the US? Please consider in your discussion each of the following as they pertain to X-SCID and other forms, such as ADA-SCID:

a) Consideration of risk/benefit of gene therapy vs. alternative therapies;

b) Revisions to informed consent documents;

c) Alterations to the cell dose administered;

d) Alterations to the vector dose administered;

e) Mapping of vector insertion sites on all clinical lots of cells prior to release for clinical use;

f) Alterations in vector design (i.e., SIN vectors)

a) Risk/Benefit

- Exclude patients with HLA identical donors
- Haploidentical transplants
  - Up to 90% survival if transplant is in newborn period
  - 50-75% when transplant is later in life (varies with transplant center)
  - Still do not get B cell reconstitution; require IgIV
  - Quality of life for “surviving” patients often sub-optimal – recurring infectious episodes.

a) Risk/Benefit, continued

- Cancer treatments often carry risk of secondary cancer
  - "If we threw out every therapy in cancer that could cause cancer, we'd get rid of some of our most effective therapies."
  - Perform family pedigree to characterize subject population

a) Risk/Benefit, continued

- Risk of gene therapy
  - If no gene transfer occurs, gene therapy is safe!
    - So previous trials aren't useful for risk assessment.
  - Don't really know, even for this trial
    - With more time, may increase or decrease
    - Need to do analysis by person-years, not just number of patients
    - Fischer trial, 100% survival
    - Success of Fischer may be related to the fact that he treats de novo, not in failed transplant patients. Shouldn't be considered a "salvage" therapy.

Trials should proceed.

b) Informed Consent

- Already include mention of risk of insertion, need more explicit statement of this event.
- All retroviral vector clinical trials should have revisions in informed consent documents to reflect this event.
- Needs to be complete, accurate, common language, full disclosure of positive and negative outcomes. Potent and direct. (IOM Report)
- Do not include mitigating factors, such as multiple hits, or the number of patients treated.
- Err on the side of saying the gene therapy caused the leukemia.
- Emphasize unknown quality.

c) Cell Dose

- If use cord blood, can reduce numbers and maintain engraftment: 1×10^5 $CD34^+$
- Other sources $\geq 2 \times 10^6$ $CD34^+$
- Design study to investigate issues of cell dose and engraftment. Rejected based on 30 years' experience, and risk to children.
- Better targeting of HSC to reduce cell dose.
  - Research issue

d) Vector Dose

- Research question.
- Currently reaching one copy per cell; not an issue.
  - Note: May become an issue with novel vectors that reach higher copy numbers in target cells.

e) Insertion Site Mapping, lot release

- Not scientifically or technically feasible to identify integration sites as lot release – REJECTED.

Insertion Site Mapping – Analysis of Patients' Samples Strongly Recommended

- Since we can't evaluate the risk accurately, we need to watch carefully.
- Close monitoring for outgrowth of single clone
  - Data collection will allow determination of frequency of monoclonal outgrowth vs. cancer.
- Once you have a monoclonal integrant, you can sequence, perform additional phenotypic analyses.
  - Knowledge of the integration site *may* inform clinical treatment – may allow earlier treatment.

Insertion Site Mapping, Continued

- Recommended time intervals:
  - Based on patient and mouse data, every 3-6 months
  - Archiving of samples – Rejected.
  - If no signal, then no need
  - Each protocol needs to develop a monitoring plan, including the trigger points for additional analyses
- Allow flexibility in monitoring plan, allow sponsor opportunity to justify not performing the monitoring.

f) Vector Design

- Important research question
- Develop preclinical models to assess risk of vector insertion for new vectors designs.

FDA/CBER Recommendations
Following Advice of BRMAC

- Revision to Informed Consent Documents in all clinical trials using retroviral vectors
- Requesting sponsors to develop monitoring plans to analyze patient samples for vector integration clonality
  - In trials where the target cells are stem cells
    - Long-lived
    - High proliferative capacity