DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Center for Biologics Evaluation and Research
Biological Response Modifiers Advisory Committee

SUMMARY MINUTES
Meeting #33, October 10, 2002
Hilton Hotel, Gaithersburg, MD

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GUESTS/GUEST SPEAKERS
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Rosanna L. Harvey

EXECUTIVE SECRETARY
Gail M. Dapolito

*not attending

The summary minutes for the October 10, 2002 meeting of the Biological Response Modifiers Advisory Committee were approved on December 2, 2002.

I certify that I attended the October 10, 2002 meeting of the Biological Response Modifiers Advisory Committee and that this report accurately reflects what transpired.

Gail Dapolito, Executive Secretary

Daniel R. Salomon, M.D., Chair

FDA BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE
SUMMARY MINUTES
MEETING #33, October 10, 2002

The Biological Response Modifiers Advisory Committee (BRMAC) met on October 10, 2002 at the Hilton Hotel, Gaithersburg, MD. In open session, the committee discussed safety issues recently identified related to retrovirus vectors in gene therapies for the treatment of patients with severe combined immunodeficiency and receive updates. The committee also received updates of CBER research programs in the Laboratories of Molecular Tumor Biology and Gene Regulation. The committee met in closed session to discuss individual research programs in the Center for Biologics Evaluation and Research.

Daniel Salomon, M.D., Chair, called the meeting to order and introduced the members, consultants, guests and guest speakers. The executive secretary read the conflict of interest statement into the public record. This statement identified members and consultants of the committee with an appearance of a conflict of interest, who were issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

The FDA provided a brief introduction to 1) an adverse event recently reported in a retroviral gene therapy trial in France for the treatment of children with X-linked severe combined immunodeficiency (X-SCID), 2) similar trials in the U.S. and 3) specific questions posed by the FDA for committee discussion.

Guest experts provided presentations to the committee on:

- a retroviral gene transfer trial in France to treat children with XSCID and the subsequent detection and confirmation of T cell expansion in one patient related to the therapy
- alternative therapies, including bone marrow transplant for patients with SCID
- historical overview of insertional mutagenesis and cancer
- mouse model of insertional mutagenesis and examples of myeloid leukemia following retroviral gene transfer in a murine model
- the role of the LMO2 gene/gene product in hematopoiesis and leukemia

The chair then commenced the open public hearing. The committee heard comments from the audience representing the views of families of X-SCID and other gene transfer patients and from advocacy groups including the Stop ALD Foundation, Citizens for Responsible Care in Research and the Council for Responsible Genetics. The committee also heard a presentation on self-inactivating LTRs from a representative of Genetics Pharmaceuticals.

Following the open public hearing, the committee began deliberations of questions posed by the FDA related to the safety of current U.S. retroviral gene transfer trials of patients with X-SCID.

Based on the committee comments that followed each of the preceding expert presentations, the Chair charged the committee to consider, in their discussion of the following question, 1) the safety, feasibility and appropriateness of proceeding with gene therapy trials in patients with different forms of SCID, 2) increased efforts for early diagnosis and 3) methods to make gene therapy safer.

The committee began deliberations on the following multipart question:

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

The committee reached consensus on the following:

1. The T cell clonal expansion (leukemia-like disease) seen in one of eleven X-SCID patients treated with an ex vivo gene therapy was likely caused by an insertional mutagenesis effect of the retroviral vector used in the gene therapy.

2. X-SCID patients with HLA identical donors, should be excluded from current X-SCID gene transfer trials because of the relatively high clinical success of intervention by HLA identical bone marrow transplantation (i.e. up to 90% survival if transplant is done in the newborn period).

3. In comparison, it was noted that for those children with only haploidentical bone marrow transplants that the benefits are not as great (i.e. 50-75% survival, the potential of requiring life-long IV Ig therapy, increased infection risks and uncertain quality of life). Thus, relative to haploidentical stem cell transplantation it is reasonable to consider gene therapy as an alternative.

4. Retroviral gene transfer trials in the U.S. should proceed only with careful consideration of inclusion/exclusion criteria that will in the best judgment of investigators, reviewers and institutional review boards provide sufficient levels of benefit over risk relative to alternative medical therapies. Moreover, informed consent documents should appropriately reflect the new information from the French X-SCID study on the potential of insertional mutagenesis with retroviral vectors

The committee also offered several viewpoints in the discussion of the appropriate patient population for X-SCID gene transfer trials:

1. Gene transfer trials as salvage therapy:
    - limiting gene therapy to X-SCID patients who first fail haploidentical transplantation could deny many patients the opportunity of gene therapy and is not advisable

    - the patients in the Fischer trial were not transplanted prior to the gene transfer, thus, it is possible that the excellent results are in part due to this selection. Therefore, it is important to consider the possibility that this particular gene therapy might not be as good an approach if used as a "salvage" therapy for X-SCID patients that have failed transplants.

2. Patient's families should have "an array" of choices with a best effort at accounting for risks and benefits vs. an either/or situation.

3. Risks of secondary cancer are not limited to gene transfer therapies – accepted cancer treatments (i.e. radiation or chemotherapeutics) often carry an increased risk of secondary cancer.

b) <u>Revisions to informed consent documents</u>

The committee agreed on the following:

1. It is important for investigators to inform all patients presently enrolled in or candidates for retroviral gene therapy trials, that there was an adverse event in a retroviral gene therapy trial and this was due to insertional mutagenesis. Informed consent forms should include strong, non-equivocal language about the retroviral insertion.
    - all retroviral vector clinical trials should have revisions in informed consent documents to reflect this event
    - ideally, all the revised consent documents should use consensus language clearly describing the event and its implications as a risk element

2. There is a need for final implementation of a comprehensive database (managed by NIH and FDA) to follow gene therapy patients and allow for dissemination of this information.

3. Informed consent documents should:
    - include consensus language that is complete and accurate

- be potent and direct; written in common language
- include full disclosure of positive and negative outcomes

- not include mitigating factors such as multiple hits or the number of patients treated
- emphasize unknowns (ex. role of family pedigree) but include information saying the gene therapy caused leukemia in a gene therapy for X-SCID.

c) Alterations to the cell dose administered

The committee discussed the theoretical potential of reducing the risk of an insertional mutagenic event by altering the number of $CD34^+$ cells that are exposed to the vector, thereby reducing the number of virus hits that could lead to an insertional mutagenic event but still maintain engraftment. The committee discussed the current standard of = $2x10^6$ $CD34^+$ cell/kilogram for engraftment as well as alternate therapies using cord blood that maintain engraftment using $1x10^5$ $CD34^+$/kilogram.

The committee reasoned that alterations of the cell dose to a level below that known to result in inefficient engraftment may pose a greater risk to the subject than the risk of insertional mutagenesis. Therefore, they did not recommend alterations to the cell dose from current standards of treatment. The committee encouraged further research on how to improve the purification techniques of hematopoietic stem cells and any other strategies, that might allow for lower target cell doses or reduce the risk of insertional mutagenesis.

d) Alterations in vector dose administered

The committee received information that current vector doses reach approximately one copy per cell. The committee agreed no change was recommended to the current vector dose.

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

The committee agreed that lot release mapping of vector insertion sites was not scientifically or technically feasible and is not recommended.

In a further discussion of safety modifications to existing SCID protocols, the committee strongly recommended monitoring for proviral integration and clonal (monoclonal, oligoclonal, polyclonal) outgrowth of subjects samples after engraftment. The committee stated assays are currently available to monitor proviral integration and should be included in all X-SCID retroviral vector gene

transfer protocols at defined time intervals (ex. every 3-6 months). It was noted that once a monoclonal integrant is identified that the genomic sequence at the site of vector integration should be determined and compared to existing genomic databases. The committee expressed that knowledge of the insertion site may, in some cases, inform clinical treatment or earlier intervention.

There was consensus by the committee that monitoring programs be developed and included in all retroviral gene transfer trials. However, the committee also stated flexibility should be allowed in the development of monitoring plans and sponsors have the opportunity to justify if monitoring for integration and clonal outgrowth are not necessary.

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

The committee agreed while this is a very important research question, they do not recommend changes to current vector design. The committee did suggest several areas of interest that could be important in the future, such as developing a vector "suicide system" and refinements in the enhancer element of the LTR.

This completed the committee discussion of safety issues related to retroviral gene therapies for the treatment of patients with severe combined immunodeficiency. The committee reconvened after a short break and heard updates on CBER research programs in the Laboratories of Molecular Tumor Biology and Gene Regulation. Following the research updates the open session of the meeting was adjourned.

For more detailed information concerning the open session presentations and committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at http://www.fda.gov/ohrms/dockets. Please submit all external requests to the FDA Freedom of Information Office.