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Workshop on Long-term Follow-up of Participants in Human Gene Transfer Research

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On June 1-2, 2004, staff from government agencies, principal investigators (PIs), and industry representatives gathered in Minneapolis just prior to the 7th Annual Meeting of the American Society of Gene Therapy (ASGT) for a workshop to discuss issues pertaining to the long-term follow-up (LTFU) of participants in human gene transfer research. The ASGT co-sponsored this workshop, along with the FDA's Center for Biologics Evaluation and Research (FDA/CBER), the NIH's Office of Biotechnology Activities (NIH/OBA), the Biotechnology Industry Organization (BIO), and the Pharmaceutical Research and Manufacturers of America (PhRMA). Workshop goals comprised (a) identifying the scientific, clinical, ethical, and social challenges associated with long-term follow-up of individuals enrolled in clinical studis of human gene transfer and (b) gathering input from workshop attendees regarding practical options for the collection of LTFU data that will be used to improve the safety of clinical gene transfer procedures. This article summarizes the presentations and overall outcomes of breakout sessions focusing on clinical, scientific, animal model, and legal/social/ethical issues.

Introduction

Stephanie Simek (FDA/CBER) began the meeting by providing an overview of the FDA's LTFU recommendations as well as the purpose of the workshop. Prior to 2000, the FDA requested LTFU of subjects who received products containing retroviral vectors or that had been exposed to such vectors; however, the death of an individual participating in an adenoviral gene transfer clinical trial led the FDA to reassess their guidelines to better ensure the safety of study subjects. Three consecutive meetings of the federal committee that advises the FDA/CBER, the Biological Response Modifiers Advisory Committee (BRMAC), were convened to obtain input regarding what type of gene transfer clinical trials necessitated LTFU as well as what type of LTFU should be performed. Based on BRMAC deliberations, CBER made the following recommendations for LTFU of subjects participating in gene transfer clinical trials: (1) All human gene transfer clinical trials should include LTFU for fifteen years with results submitted annually to the FDA, (2) LTFU should focus on the collection of clinical information, especially pertaining to *de novo* cancer, neurologic, rheumatologic, and hematologic/immunologic disorders, and (3) LTFU for the first five years should include an annual physical exam, whereas data for years six through fifteen could be collected by a clinical questionnaire. Dr. Simek explained that the current workshop was designed to help participants gain an accurate understanding of the current FDA recommendations on LTFU and, through group discussions, to enable the FDA to receive feedback on ways to improve the current LTFU framework to improve human gene transfer clinical trial safety while promoting opportunities for product development.

Data Monitoring Registries

To illustrate the utility and the potential pitfalls of collecting LTFU data on subjects in gene transfer trials, examples of two long-term data monitoring registries were presented. Dr. Mary Horowitz, Scientific Director of the International Bone Marrow Transplant Registry/Allogeneic Bone Marrow Transplant Registry (IBMTR/ABMTR), described the database cataloguing LTFU information on patients receiving bone marrow transplantation. Started in 1970, the IBMTR registry currently includes more than 80,000 observational records with contributing research centers spanning the globe. Numerous research groups have analyzed the data available in the IBMTR registry to determine the long-term mortality after transplantation; specific, low frequency complications and associated risk factors; and the long-term quality of life of patients and spouses. Dr. Horowitz concluded by stressing that "registries are an important tool for studying late effects of therapy." She also noted that, "Follow-up of treated patients is difficult but possible with adequate funding and an organized approach."

Mr. Neal Mantick, Director of the Global Registry Programs, Genzyme, Inc., then presented a second example of an LTFU database: the Gaucher Registry. This database was created as a phase IV FDA study requirement for drug approval of enzyme replacement therapy (EZT), a treatment for this extremely rare genetic disease. Genzyme has continued the registry past the required timeframe based on its effectiveness in increasing disease awareness and understanding for the larger medical community, assisting expert physicians develop recommendations for monitoring and treating patients with this disease, and helping to evaluate the long-term effects of EZT. Mr. Mantick summarized his talk by stating that registry programs are "important tools

for establishing the significant clinical databases necessary for sustained research to improve patient care."

To this end, LTFU data on gene transfer research subjects are currently being collected in the Genetic Modification Clinical Research Information System (GeMCRIS) database (www.gemcris.od.nih.gov)—a joint effort by the FDA and NIH. As stated on the GeMCRIS web site, "GeMCRIS is a comprehensive information resource and analytical tool for scientists, research participants, institutional oversight committees, sponsors, federal officials, and others with an interest in human gene transfer research…[that] allows users to access an array of information about human gene transfer trials registered with the NIH."

Scientific Issues

Carolyn Wilson (FDA/CBER) introduced the scientific issues regarding the long-term risks of human gene transfer research by focusing on those properties of gene transfer systems with the potential for long-term risks, including the persistence of vector sequences, integration of the vector into host genomic DNA, and transgene-specific effects. Dr. Wilson posited that the long-term risk due to vector persistence would be most strongly affected by whether the vector integrates. Preclinical studies could be used to assess the potential for vector persistence and, if observed, vector integration. Regarding the risks due to integration, Dr. Wilson addressed whether dysregulated gene expression would necessarily lead to tumorigenesis. Recent data from several studies of replicating retroviruses indicate that the transcriptional profile of the transduced cell may influence the tumorigenic potential of the integrating virus. It remains to be determined whether these results will directly pertain to the related replication-defective retroviral vectors, well-known to have the highest potential for genomic integration among all gene transfer vectors used to date. She concluded by discussing transgene-specific effects associated with experimental human gene transfer, such as tumorigenic effects of the transgene itself, the induction of autoimmune disease in genetic disorders, adverse effects caused by constitutive transgene expression for a normally tightly regulated gene, and the potential for complications when the transgene is expressed in cell types where the endogenous gene is not normally expressed (*e.g.*, a liver-specific gene expressed in blood cells).

Barrie Carter (Targeted Genetics Corporation) spoke on the properties of gene transfer systems with little or no potential for long-term risks. He began by stating that vector genomes are not mutagenic *per se*; it is their potential for integration that may be mutagenic. Consequently, the mutagenic potential of a certain vector should be based on its frequency of integration and the frequency of mutant phenotypes caused by integration. Dr. Carter presented several pieces of published data demonstrating that adeno-associated vectors (in which the specific integration system has been deleted) and plasmids have little potential for integration—well below the spontaneous mutation rate—and he concluded that these vectors pose little to no long-term risk in study subjects.

Clinical Issues

Daniel Rosenblum (FDA/CBER) discussed the clinical issues associated with LTFU of gene transfer subjects. He first presented a detailed list of the FDA recommendations for clinical follow up. The FDA recommendations can be found in a standard letter to sponsors of gene transfer trials that requests their acknowledgement that a long-term clinical monitoring protocol is in effect. The sponsor is asked to provide sufficient details to indicate that monitoring is consistent with recent advice and recommendations provided to the FDA by BRMAC (see http://www.fda.gov/ohrms/dockets/ac/cber01.htm#Biological%20Response). The recommendations that emanated from the BRMAC meetings advise sponsors/PIs to submit annual clinical LTFU data for all subjects enrolled in gene transfer studies. The clinical observations may be made by any physician or designated third party, but it is the sponsor's obligation to gather the information and report it to the FDA. Subjects should be monitored for adverse events for fifteen years, with particular attention paid to higher risk outcomes such as new malignancies, neurologic disorders, autoimmune disorders, and hematologic disorders.

Dr. Rosenblum stressed that the recommended physical examination of subjects for the first five years following gene transfer should include at least a medical history, an examination of appropriate organ systems, and a hemogram. The recommended follow-up is intended to document established disorders, not to search for evidence of undiagnosed syndromes. During the subsequent ten years of LTFU, a one-page questionnaire or postcard may be adequate for reporting any events related to the five areas of concern stated above. If serious or unexpected adverse events arise, expedited reporting to the FDA and NIH is required. Dr. Rosenblum stated that the current LTFU recommendations apply to all clinical trials involving gene transfer—that is, *all* vectors, *all* diseases, and *all* subjects. He did note, however, that the recommendation is intended to encourage collection of long-term safety data. A sponsor could propose an alternative LTFU plan for trials in which it is extremely unlikely that subjects will survive for fifteen years or in which they have multiple co-morbidities and exposures that will interfere with the collection of such data.

Terence Flotte (University of Florida) then followed by briefly stating that the aims of collecting and analyzing the LTFU data are to (a) assess the safety of human gene transfer by allowing analyses of data within and across trials and (b) identify any associated adverse events based on transgene/protein expression and the vector used. Dr. Flotte then facilitated the transition to the breakout sessions by reviewing the questions that would be discussed, stressing that these sessions represented the ideal forum for all atten-

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dees to voice their concerns and opinions on the various topics regarding LTFU.

Scientific Issues: Breakout Session

The scientific issues breakout session was co-moderated by Barrie Carter and Carolyn Wilson. The goal of this session was to answer a major question: Is there a scientific basis for determining the extent and type of LTFU required in different human gene transfer clinical trials? The assumption that the potential for long-term risk of a clinical gene transfer system will be most strongly influenced by integration of the vector into the genome, vector persistence, and transgene-specific effects was discussed. The audience agreed that if there is no vector persistence, then the long-term risk from this factor is analogous to that of any new drug. Some participants thought that the transgene would be a stronger determinant of long-term risk in those cases where vector persistence is observed. All agreed that integration frequencies associated with replicating retroviruses pose the greatest risk to study subjects, but even in this scenario, many thought it was important to recognize that not all integration events are equivalent. For example, integration close to or within a genetic locus would have a greater biological risk effect than integration in intergenic regions of the genome. Consequently, when determining integration frequency thresholds, it was suggested that all integration events be assumed to occur within genes. This frequency could be compared with the endogenous rate of genetic change, such as rates of mutation, retrotransposition, or chromosomal translocation, to determine the relative risk of a particular vector system.

Because all aspects of vector administration—route, mode, dose—will impact the vector integration frequencies, the majority of participants agreed that preclinical studies should be used to carefully assess the degree of vector integration for a particular gene transfer system. When considering *ex vivo* human gene transfer clinical trials, many felt that protocols using short-lived transduced cells would not require LTFU, whereas LTFU should be considered when treating subjects with long-lived cell populations (*e.g.*, hematopoietic stem cells) and LTFU should continue, if feasible, as long as the transduced cells are detectable. Although some audience members argued that persistence in the absence of vector integration would not be sufficient to merit LTFU, others contended that certain routes of administration, such as direct administration of a vector to the central nervous system, may carry sufficient risk to warrant LTFU if unintegrated vector persistence is observed.

Turning to risks associated with specific transgenes, the majority concurred that it would be difficult to devise a system to categorize and assess the risk related to a specific transgene in any given trial due to the context-dependent effects of transgene expression (*e.g.*, the potential for long-term risk may differ greatly depending on the cell type and/or age in which the transgene is expressed). Acute toxicity of the transgene should be evident from routine preclinical studies, and biodistribution studies would help reveal the levels and tissue specificity of transgene expression, which could then be compared with its endogenous gene expression. In cases of vector persistence or ectopic gene expression, participants suggested that the long-term toxicity of a particular transgene should be concurrently studied using animal models, where possible, while the phase I clinical trial is performed.

Most of the participants in this session felt that it is an undue burden to perform LTFU on subjects participating in early-phase trials unless there is some indication that the human gene transfer provides a beneficial biological effect. Others noted that some subjects (*e.g.*, those with cancer) would likely seek additional treatment before or after human gene transfer, and these treatments would have their own inherent long-term risks that would complicate the interpretation of LTFU data. In considering the many LTFU variables discussed during this session, it was asked whether LTFU could be dictated using a tiered approach or whether case-by-case assessments must be made. The general consensus was that if a sponsor provided data to address the risks associated with vector persistence, the vector integration frequency, and transgene-specific effects, then a case-by-case review of these data by the FDA could determine whether a default of fifteen years of LTFU should be implemented.

Clinical Issues: Breakout Session

Stephen Rose (NIH/OBA), Daniel Rosenblum, Terence Flotte and Philip Noguchi (FDA/CBER) co-chaired the breakout discussion on clinical issues. Regarding the fifteen years of LTFU data collected on subjects enrolled in human gene transfer trials that is to be reported to the FDA, participants in this session sought a better understanding of what data should be collected, and who should collect and interpret the data. In response to numerous questions from the audience, representatives from the FDA clarified the fifteen-year LTFU recommendations. They explained that all IND trials must devise a plan for reporting LTFU data, which must meet FDA approval. It was stated that LTFU involves only the reporting of observations; it does not necessitate the provision of long-term care to study subjects, nor is it a specific, in-depth program of evaluation for occult clinical *sequelae*.

Many audience members called into question the value of reporting LTFU data, especially given the limitations inherent in early-phase trials (*e.g.*, small sample size, low dose, etc.) and because the data might be of limited value with no corresponding control data. The FDA, NIH, and others responded with an often-heard refrain during the workshop: "You don't know what you don't know." Given the responsibility to inform the public regarding the risks associated with any experimental treatment, they felt LTFU data are needed to help identify possible risk trends. NIH representatives stressed that the LTFU data reported to them are

being stored in the GeMCRIS database where the data will be analyzed. To obtain the most valuable LTFU data possible for analysis, the majority of audience members said that it would be most effective to obtain follow-up data from trials in later phases when the experimental product is likely to be licensed—a point that the FDA said it would take into consideration with the possible exception of those products in which the rate of vector-mediated insertional mutagenesis is known to exist (*i.e.*, with retroviral vectors).

Turning to who should collect the data, participants came to a consensus that the sponsor is ultimately responsible for ensuring that LTFU data are collected; however, the sponsor can delegate others to acquire or report the data (*e.g.*, primary care physicians, subject self-reports, third parties). Participants also agreed that a contingency plan should be in place to ensure consistent LTFU reporting for the fifteen-year duration should the responsible party vacate their position or go out of business.

Long-Term Animal Models: Breakout Session

The long-term animal models discussion was co-moderated by Theresa Chen (FDA/CBER) and Cynthia Dunbar (NIH/National Heart, Lung, and Blood Institute). The discussion focused on the design of long-term preclinical studies using animal models, the potential timing of these studies relative to product development and clinical investigation, and the possible ways that the resultant data should be published. The audience agreed that long-term preclinical safety studies should be performed in animal models of the disease under study, when possible. However, it was noted that some of these animal disease models have limited life expectancies compared with healthy animals, and that the latter would be more suitable for acute toxicity and efficacy studies. Although physiologically more akin to humans, many thought that the use of large animals (*e.g.*, nonhuman primates) for preclinical studies would only be informative in those instances where high-frequency events are expected due to the typically small sample sizes. In contrast, smaller animal species (*e.g.*, rodents) would be more suitable for long-term safety studies requiring larger sample sizes, although no extrapolation/translation to an equivalent human lifespan could be given. Regarding the choice of dose in long-term safety studies, most participants commented that the use of the highest nontoxic dose possible is appropriate for acute toxicity studies but not for long-term toxicity studies. Hence, long-term toxicity studies should use clinically relevant dose levels (*i.e.*, where activity/efficacy is observed), not the maximally tolerated dose based on short-term toxicity studies. Moreover, the audience thought that the studies should be designed on a case-by-case basis to include defined endpoints for *post mortem* examination in order to yield useful information.

In regard to the timing of animal studies, most participants believed that they should be performed in parallel with the phase I clinical trial, particularly if the study uses large animal species. To disseminate these results, most session members thought that the data generated from basic research surrounding the IND should be published or presented in a peer-reviewed forum in addition to timely communication of relevant information to the affected sponsors. The open-ended question is whether any organization, such as ASGT, will be able to create and maintain a public database of preclinical study results, as has been proposed, thereby allowing open access to interested parties. The final consensus among participants was that if animal study results demonstrate a need to do LTFU in humans, then animal studies of long-term duration may have served as a valuable tool.

Legal, Social, & Ethical Issues: Breakout Session

The final breakout session combined legal, social, and ethical issues related to LTFU and the associated risks stemming from gene transfer. Mr. Lewis Grossman (Washington College of Law) and Ms. Hilary Schock (Merck) co-chaired the legal portion. Mr. Grossman began by noting that the FDA LTFU recommendations are really requirements and should be regarded as such. He stated that although the FDA has no formal authority to enforce compliance with these particular recommendations, they can effectively ensure that sponsors/PIs comply by withdrawing or imposing clinical holds or by rejecting applications for drug approval based on "lack of data." In turning to subject privacy issues, Ms. Schock outlined the privacy and data protection laws that apply to LTFU data collection from individuals, including the Health Insurance Portability and Accountability Act (HIPAA) and state medical privacy and genetic privacy laws. She described tools to facilitate LTFU data collection, including subject education and coordination across study sites, and discussed language that could be used in subject permission documents that would facilitate LTFU, such as detailing the design and purpose of sample collection and the requirements for annual physicals/clinical questionnaires.

Proceeding to social and ethical issues, James Childress (University of Virginia) and William Allen (University of Florida) echoed similar ideas by suggesting that sponsors/PIs adopt the mindset that the individuals involved in gene transfer studies are collaborators in the research process rather than objects/subjects of study. This would engender respect between all parties to build a community of trust to facilitate LTFU data collection. By educating study subjects about the value of these data, not only can general scientific knowledge be gained but their long-term health can also be monitored. Ms. Lora Kutkat (NIH) provided a brief overview of HIPAA, the regulations for collecting subject information while protecting their anonymity, obtaining informed consent from healthy subjects as well as those with impaired decisional capacities, and the regulations regarding using and providing LTFU data to others. More information on HIPAA issues can be found at

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www.hhs.gov/hipaaprivacy/research/.

Audience discussion focused primarily on legal issues, such as who assumes responsibility for LTFU data collection if the primary sponsor/PI unexpectedly vacates this position. Several different possibilities were suggested, but, above all, it was stressed that the sponsor/PI should have a contingency plan in place before the study starts to assure study integrity and subject safety. Similar to an insurance policy, it was proposed that sponsors provide a surety bond to assure that their LTFU efforts continue as detailed in their contingency plan. To that end, the audience suggested that perhaps small companies specializing in LTFU on behalf of sponsors/PIs could be started and/or that subjects be given the option to report their annual follow-up data directly to the GeMCRIS database. In addressing whether research subjects should be excluded from gene transfer trial participation if they do not agree to LTFU, the audience agreed that a clause should be included in the subject's informed consent document stating that subjects would be expected to partake in LTFU; however, all agreed that subjects have the right to withdraw from a study if they choose to not abide by the LTFU provision.

Group Discussion:
Reassessment of LTFU Recommendations

All workshop participants reconvened following the breakout sessions to address the following question: What information would bring about a reassessment of the requirements for LTFU in a particular class of human gene transfer clinical trials? During the ensuing discussion, a piece of pertinent information emerged: As stated by the NIH, since 1990, approximately 5,000 adverse events have been reported. Accordingly, the NIH and FDA stressed that being conservative regarding LTFU monitoring is important until they have excluded significant long-term risks due to gene transfer. A robust plan has been developed to analyze the GeMCRIS data, and the findings will be made available to the public. Audience members expressed concern that data lumping during analysis might find untrue trends because study design nuances would not be considered. NIH representatives addressed this issue by explaining that the GeMCRIS database has been designed with the flexibility to independently track different properties of a gene transfer system such as the vector, transgene, route of administration, and clinical indication. NIH representatives indicated that any trends identified could be analyzed by different sets of criteria to determine their validity.

Meeting Summary

During the closing remarks, the FDA stated that the workshop was very helpful in providing input into the concerns surrounding the issue of LTFU of subjects in gene transfer research. Moreover, the FDA will develop a guidance document for LTFU of subjects in gene transfer clinical trials given an overriding concern voiced at all breakout sessions regarding the need for enhanced education of sponsors/PIs as to what type of LTFU information is needed and who is responsible for submitting this information to the FDA. One unresolved issue identified in this workshop is when to initiate LTFU during product development. Many participants voiced concerns that early-phase data will be of little value given the small sample size and low doses administered and, hence, that LTFU data should not be collected until later phases of clinical investigation when a biological effect has been observed and there are a larger number of subjects with appropriate controls. However, there was overall agreement that sponsors/PIs administering vectors with known integration events at or above background mutation rates should continue collecting LTFU data at the initiation of clinical trials.

All summary slides for this workshop can be found at www.asgt.org.

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