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Commentary

Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency

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ABSTRACT

It has been 9 years since Mr. Jesse Gelsinger died from complications of vector administration in a liver gene therapy trial of research subjects with a deficiency of ornithine transcarbamylase (OTCD). This study was performed at the Institute for Human Gene Therapy of the University of Pennsylvania (Penn) which I directed. His tragic death provoked a series of events that had implications beyond those directly involved in the clinical trial.

The events surrounding the death of this research subject have been the topic of much coverage and commentary in the popular press. The goal of this article is to share with you my reflections on the OTCD gene therapy trial and lessons that I have learned which may be of value to others engaged in various aspects of translational medicine.

The Phase I Gene Therapy Clinical Trial for OTCD

The gene encoding OTC is located on the X chromosome, meaning that males are more commonly affected with the disorder (reviewed in [1]). A complete absence of OTC function due to a severe mutation in its gene can have dramatic clinical consequences. Newborn males with a complete deficiency develop hyperammonemic coma following their first 3 days of life which, if untreated, is lethal. Even with current treatment, most survivors are left with severe cognitive deficits. Individuals who survive the newborn episode of coma can be partially treated with chronic drug therapy, although they are at risk for repeated episodes of protein-induced coma; the overall prognosis, despite excellent clinical care, is poor, and leads to the development of progressively worsening cognitive abilities and premature death in childhood. Females who carry one abnormal gene for OTC are usually without symptoms, although they can demonstrate protein intolerance especially at times of severe stress, such as following major trauma. Intermediate phenotypes are observed with males who have OTC mutations that render the enzyme partially defective.

The metabolic and clinical consequences of a deficiency of OTC can be corrected through liver transplantation, although there is significant morbidity and mortality from the procedure and the ongoing immune suppressive drugs [2]. Interestingly, the liver in patients with OTCD is generally normal except for the defect in this one gene. This suggests that an alternative approach to treating OTCD would be correction of the genetic defect or replacement with a normal version of the OTC gene in hepatocytes.

I was recruited to Penn in 1993 to establish the Institute for Human Gene Therapy. Soon after my arrival, I met with Dr. Mark Batshaw, who is a world expert in metabolic diseases with a particular interest in OTCD. Dr. Batshaw, together with his collaborators at Johns Hopkins University, developed the current pharmacologic therapy for OTCD [3]. We agreed that this disease would be an excellent initial model for testing liver-directed gene therapy and we initiated a collaboration to evaluate this possibility.

At the time of my recruitment to Penn, the field of gene therapy was still in its infancy. The first clinical trial of gene therapy for a genetic disease had been initiated, only 3 years prior to my recruitment, by Drs. Anderson and Blaese in research subjects with an inherited immune deficiency disease. Our studies would be the first to evaluate gene therapy directed to liver in humans with a genetic disease by direct administration of a vector. We were well equipped to develop the basic science and preclinical research to evaluate the feasibility of gene therapy for OTCD. The challenge, however, was to access the translational resources necessary to bring our basic research conducted in the laboratory into the clinic in the setting of first-in-human Phase I clinical trials. One approach to access these resources is through collaboration with the biopharmaceutical industry, which is more experienced than academia in issues related to translational and clinical research. This, however, was difficult to achieve in the early 1990s due to the nascent state of the field of gene therapy and the fact that OTCD was not a sufficiently large market to justify much commercial investment. Our approach, therefore, was to establish a translational capability internal to the academic program at Penn which would include production of clinical grade vector under good manufacturing practices, evaluation of the safety of the vector in animal models under good laboratory practices, design and conduct of the

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clinical trial under good clinical practices, and a quality assurance oversight group to assure compliance in all of these critical areas. This is, in fact, what we attempted to develop in the 1990s within the Institute for Human Gene Therapy. At the time the OTCD trial was put on hold in the Fall of 1999, the Institute for Human Gene Therapy was directly supporting Investigational New Drug protocols (INDs) for seven clinical trials spanning a wide range of diseases.

The key step in advancing gene therapy for OTCD was to develop a gene delivery vehicle capable of shuttling a normal version of the OTC gene into hepatocytes. This was accomplished through the use of an attenuated or disabled version of an adenovirus which had been engineered to express the normal OTC gene. Dr. Batshaw and I were able to demonstrate some level of efficacy using an adenoviral vector in a mouse model of OTCD [4,5]. Based on these preliminary data, we assembled a team of investigators to further this program and submitted a Program Project Grant to the NIH to support the work. Responsibilities were distributed amongst three scientists with complementary backgrounds in order to access the scientific and clinical experiences necessary to: (1) perform the preclinical studies, (2) to conduct the clinical trial, and (3) to manage financial and non-financial conflicts of interest of the investigators. A more thorough discussion of these conflicts of interest is provided in later sections of this commentary. I provided expertise in vectors and preclinical gene therapy and served as sponsor of the IND application to the FDA and was co-Principal Investigator on the grant. Dr. Mark Batshaw is an expert in OTCD and a practicing pediatrician. He served as Principal Investigator on the Institutional Review Board (IRB) submission to the affiliated pediatric hospital, The Children's Hospital of Philadelphia, and was the Principal Investigator on the grant to the NIH. We recruited the help of a colleague of ours, Dr. Steve Raper, who is a general surgeon and had experience in clinical gene therapy for treating liver disease using an alternative approach based on transplantation of genetically modified cells. Dr. Raper was the Principal Investigator of the protocol submitted to the IRB at the Hospital of the University of Pennsylvania where the subjects were admitted; in this capacity, he served as the physician of record for these individuals while in the hospital. He was also co-Principal Investigator on the grant.

The grant was submitted on March 23, 1994 and we soon developed promising preclinical data that led to the submission of an IND to the FDA approximately 2 years later. The preclinical data developed to support this IND application involved efficacy experiments in the mouse model of OTCD and safety assessment studies performed both in mice and in various types of non-human primates. Using the first generation of the adenoviral vector (i.e., deleted of the E1 gene), we showed a nearly complete correction of the metabolic defect in the mouse model for OTCD that lasted for several weeks to 1 month [4,5]. High doses of the first-generation vector were administered to mice and rhesus macaques in order to assess potential toxicities [6,7]. The primary toxicity we observed was related to the development of self-limited hepatitis approximately 1 week after vector administration. At the highest dose of the first-generation vector, monkeys developed a syndrome of severe liver damage and a clotting disorder that led to death or required euthanasia within several days [6]. Between the time of the initial IND submission on April 18, 1996 and when we received permission to enroll subjects on October 21, 1996, we brought forward at least two improved versions of the OTC adenoviral vector called second- and third-generation vectors. The trial proceeded with the third-generation vector which showed in mice a substantially improved toxicity profile over what was obtained with the first-generation vector [8]. In an attempt to assure safety in the clinical trial, we proposed to administer third-generation vector at a maximum dose that was 17-fold lower than the dose of first-generation vector that showed severe toxicity in macaques. We felt that this would provide us with a 100- to 1000-fold margin of safety in terms of vector dose. Based on discussions with FDA, we designed a final study to simulate the clinical trial in which third-generation vector was administered to baboons at the starting and ending doses proposed for the clinical trial. Only minor and transient laboratory abnormalities were observed in the high dose baboon group [9].

The team engaged in an extensive set of discussions regarding the structure of the clinical trial [10]. Various aspects of the study design were quite standard such as the fact that it would be a Phase I dose escalation study using safety measures as the primary endpoints, although metabolic correction was also considered. We selected six groups of subjects, with three subjects per group, beginning with a very low dose vector, and escalating half-logs between cohorts to a maximum dose of vector as described above.

One controversial aspect of the trial related to the eligibility criteria for participation which was restricted to adults. Consideration was also given to enrolling newborns in the setting of, or immediately following, resolution of the neonatal hyperammonemic crisis. This was rejected based on concerns over informed consent which would have to be provided by a guardian and the "coercive" nature of the situation in which the guardian would need to provide this consent (i.e., at a time when the child is severely sick and at high risk of dying and/or becoming mentally retarded). The decision to proceed with adults followed extensive discussion with scientists, metabolic disease physicians, bioethicists, and representatives of the Urea Cycle Foundation. Our decision to focus on adults was fully endorsed at the time the protocol was initially reviewed by the relevant regulatory agencies and oversight committees. This decision was questioned after the trial was stopped because we had subjected volunteers with little to no disease-associated morbidity to vector-associated risks that were essentially unknown in humans. In fact, the bioethics community has debated the appropriateness of clinical trials in healthy volunteers in which participation is associated with more than minimal risk [11]. For example, the first evaluation of toxicity for many novel cancer treatments and some applications of gene therapy are performed in subjects more severely affected by their disease. In retrospect, I have questioned the wisdom of this decision, although beginning the study in younger, more severely affected individuals presents a different set of ethical dilemmas.

The first subject was dosed with vector on April 7, 1997. The clinical trial progressed through the first five cohorts without serious adverse events, although toxicity was indeed observed as described [10]. These toxicities included self-limited fever and flu-like symptoms and several transient laboratory abnormalities (e.g., transaminitis, hypophosphatemia, and thrombocytopenia). The first subject of the sixth cohort (i.e., OTC018) received the highest dose of third-generation vector which was 17-fold lower than the dose of the more immunogenic first-generation vector that caused severe toxicities in non-human primates. This 19-year-old female experienced the same toxicity seen in previous human cohorts that included fever and flu-like symptoms with some transient laboratory abnormalities. The second subject in this cohort was an 18-year-old male, Mr. Jesse Gelsinger[1] (OTC019). He received vector on September 13, 1999 and experienced a dramatically different response that ultimately led to systemic inflammation and multi-organ failure; this fulminate acute inflammatory response to vector was different from the toxicities observed in the other human research subjects and in the preclinical studies [12]. Despite attempts of the clinical team and all available consultants to support Mr. Gelsinger through this severe inflammatory episode, he died

[1] The name of this research subject was disclosed extensively in the popular press with the apparent consent of his family. We therefore will refer to him as Mr. Gelsinger throughout the manuscript.