The Patient's Perspective

Evaluating Gene Transfer Clinical Trials

When assessing the potential risks and benefits of gene transfer, one must recognize that gene transfer is inherently different from conventional medical treatments. Side effects and long-term risks can have entirely different criteria; indeed, many of the parameters used to evaluate conventional pharmaceutical drugs (ie, drug half-life, route of excretion or metabolites) have little or no direct meaning in a genetic-transfer context.

Contemporary pharmaceutical agents are the result of the development of chemical or protein compounds targeted to specific chemicals or other proteins in the body, which undergo laborious biodistribution and toxicology studies in animals (followed by phase I, II and III clinical trials in human subjects). With some exceptions, it is only after this exhaustive evaluation that a new drug will be considered for approval by the Food and Drug Administration (FDA) for use in general medical practice. ▶

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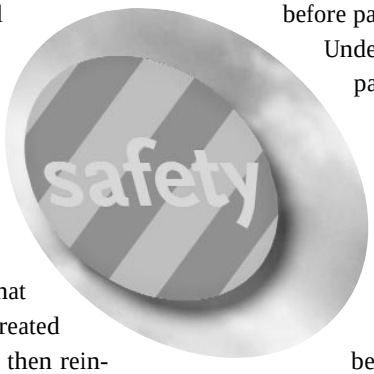
▶ The use of DNA (a gene) as a therapeutic agent makes it difficult to apply some traditional pharmaceutical parameters to determine the safety and efficacy of gene-based transfers. Past reviews of gene-based transfers for hemophilia have highlighted various gene delivery systems and the basic biology behind them (*Parent Exchange Newsletter* [PEN] 8(1), 1-11 and *PEN* 10(1), 1-9). To date, gene-based delivery systems in trials for hemophilia introduce genetic material either as episomal structures (small loops of DNA that remain separate from the cells' native chromasomal DNA) or as integrating DNA that is incorporated into the chromosomal DNA. In addition, both episomal and integrating plasmids can be introduced by viral vectors injected into a patient or directly into a patient's own cells that have been removed, treated in the laboratory and then reintroduced to the patient. All of these approaches are under continued development and refinement. Therefore, the safety and efficacy of a particular gene transfer approach will be likely to change with time.



Since standard pharmacology language does not directly apply to gene transfer, patients and the medical research community need to establish mutually-understood yardsticks for gene transfer safety and efficacy, as well as for risk assessment. The principal of informed consent requires a patient to have a rudimentary understanding of the purpose of the clinical research, including the risks and alternatives, before participating in a clinical trial. Understanding the specifics of a particular gene transfer technology offered in the clinical trial may seem overwhelming at first, but it is essential that each patient and the patient's family begin to educate themselves, as there are likely to be several options available. Several articles and videos produced by the hemophilia community will provide a useful base of knowledge of current genetic technologies directed toward hemophilia treatment. A good starting point is an online course presented by NHF at www.hemophilia.org. A series of annual articles published in the February 2001 edition of *PEN* is also a useful resource. These articles are available online at www.kellycom.com. Descriptions of how biological systems function are often referred to as paradigms and it will be useful to reproduce the pictures presented in these materials to understand the paradigm, or underlying biological system, under discussion. Despite a lack of technical expertise, all questions are valid and important and will probably have an impact on your decision making and participation in a clinical trial. Additional public forums for your questions are provided at NHF's Annual Meeting and other consumer meetings where gene transfer for hemophilia is a topic that is presented. For more information on NHF's Annual Meeting, call HANDI at 800-42-HANDI.

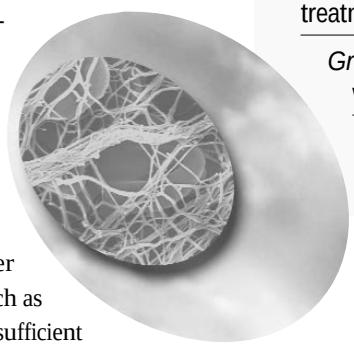
For parents contemplating a gene transfer clinical trial for their son or daughter, there is a heightened ▶

TABLE 1. SAFETY OF GENE TRANSFER
Short-term (days). Examine human and primate data demonstrating:
Tissue or organ damage due to the gene delivery method (eg, acute liver failure) *Immune response to gene delivery system* (white cell counts, high levels of certain cytokines, specifically, IL-6 and IL-10)
Long-term (weeks to months). Examine human and animal data
Tissue or organ damage (eg, longer-term liver damage) *Formation of neutralizing antibodies against vector or therapeutic gene*
Lifetime (years to decades). Examine animal data
Insertional mutagenesis and resultant cancer *Organ failure (chronic hepatitis-cirrhosis)*

Drs. Gina and Paul Shreve with their children, Stephanie and David

need to understand the risks of a particular gene transfer approach, both short-term and long-term. There are two primary issues: safety (ie, what are the side effects and risks [Table 1]) and efficacy (ie, what level of "cure" can be expected and for how long [Table 2])?

Both long-term and lifetime safety data from human subjects will be limited; so therefore, these risks must be largely inferred from animal data (Table 1). A certain gene-transfer approach may have advantages over another approach in terms of risks or the potential for long-lasting effective treatment of the bleeding disorder, and it is important that the potential on these two sides are balanced. Many parents consider it important to establish statistical evidence of long-term safety prior to the enrollment of their child in a gene transfer trial. This requires: 1) studies involving a particular gene transfer in an animal model, such as the hemophilic dog, in sufficient numbers to yield statistically significant data or 2) trials of many adult individuals, which may require ongoing acceptance of HIV and/or hepatitis C positive patients in order to garner sufficient data. Since many of these individuals have chronic liver disease, delivery systems that target the liver may be more dangerous to test in this population.



Because satisfactory factor-replacement treatments are currently available, the gene transfer treatment must show positive evidence in animals that it will work safely in humans for the patient to be motivated to utilize a genetic transfer. In general, the patient will desire a therapeutic correction that persists for as long as possible (Table 2). The patient must make a judgement of what he or she is comfortable living with as a reliable level of correction. A circulating factor level of 10% to 15% would provide some sense of a real and reliable correction. The patient must also recognize that the lack of long-term studies in humans means it will be difficult for the patient to know (when entering into a trial or treatment setting) whether he or she is likely to experience the loss of gene expression and require some additional form of treatment. It is likely that these questions will not be answered in early clinical studies, before most patients will be faced with the option of enrolling in a clinical trial. Therefore, it is important that each affected individual understands the fundamentals of genetic-transfer technology as well as each individual's tolerance for risk and personal requirements for a successful genetic-based transfer. Long-term follow-up is critical for assessing potential late risks associated with gene transfer. Those volunteering for trials should commit to long-term follow-up, which is a required part of all current trials.

While the hurdles are significant, breakthroughs will most likely occur and the payoff of effective gene transfer for many populations with inherited genetic disorders is tremendously exciting. As a community, we can do our part by educating ourselves in the language of gene transfer and discussing the hopes and expectations that we have for effective cures for inherited bleeding disorders based on genetic transfers.

TABLE 2. EFFICACY OF GENE TRANSFER

Magnitude of circulating levels of functional FVIII or FIX. Examine human and animal data demonstrating:

Detectable levels, 1% to 2% have been achieved in some patients in several trials for periods of months. Generally unsustained after weeks to months in phase I safety studies.

Stable therapeutic levels, >5% would have a significant therapeutic benefit in converting severe phenotype to mild.

>10% to 15% target may represent a highly reliable therapeutic correction

Stability and Continuity of Expression and Maintenance of Circulating Levels: Examine human and animal data for declining levels of factor.

Fluctuation is dangerous for patients who may be caught unaware without medical resources for treatment. This must be prevented for effective therapy, though knowledge of the biological basis of such fluctuations for a given treatment method may be broadly useful in improving genetic transfers.

Gradual decline in serum functional factor level may be managed, whether or not retreatment is possible.

Immune response to vector possibly preventing repeat treatment with the same vector.