6.2 Gene Therapy

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Educational Objectives

1. To understand the ethical and legal issues relating to the inclusion of children in clinical studies on gene therapy.
2. To identify allowable limits regarding the inclusion of children in these clinical studies.

Case

Twelve-year-old Felix has Duchenne muscular dystrophy (DMD). Because of the progression of the disease and the weakness of his muscles, Felix must use a wheelchair. Given that the diagnosis has been confirmed by molecular therapy techniques, which have identified the mutation in the dystrophin gene, Felix's physician, Dr. Williams, is certain that Felix's muscles will continue to degenerate rapidly. Although there are certain steroid-based medicines that can help children suffering from DMD to save their muscular strength for a certain amount of time, there is no treatment that can fight the disease.

Dr. Williams, who is also a researcher, has prepared a research project on an ex vivo somatic gene therapy to treat DMD. This therapy consists of removing myoblasts from children with the disease, modifying them genetically in a laboratory to insert the normal dystrophin gene, and re-injecting them into the child with a large number of injections to the muscle. This is still an experimental therapy with various risks for the health of participating children, such as a potential immune system reaction against the dystrophin. There is also a potential risk of tumour formation by the genetically modified cells, even if samples of the genetically corrected cells are pre-tested by transplantation in immunodeficient mice. Despite these risks, this therapy offers hope to improve the quality of life of children suffering from DMD.

Questions

1. What special challenges does gene therapy research pose?
2. Is it ever acceptable to perform gene therapy research involving children?
3. What are the benefits and harms of such research? Are they reasonable?
4. Does a child need to assent to his/her participation in the gene therapy research? If a child dissents, should his/her decision be respected?

Discussion

Q1. What special challenges does gene therapy research pose?

Gene therapy raises different challenges from routine clinical research. First of all, gene therapy must confront a significant challenge: proving its effectiveness. Although gene therapy has been successfully used to treat children suffering from a severe combined immune deficiency linked to chromosome X (X-SCID), it has also been linked to increase risks of death and cancer in research subjects. For example, in 1999, 18-year-old Jesse Gelsinger died during a gene therapy experiment at the University of Pennsylvania. Moreover, in the clinical trials of gene therapy for X-SCID, three children developed leukemia. Gene therapy is therefore still perceived as an experimental intervention involving serious risks for research subjects. Despite the fact that the number of clinical trials on gene therapy continues to increase every year, gene therapy is still far from being a part of modern medical practice. However, in the case of childhood diseases for which there are no known treatments, gene therapy could constitute the last hope for saving or at the very least improving the quality of life of afflicted children.

Another challenge faced by gene therapy is the characterization of the intervention. Some categorize it as an experiment, while others consider it an experimental therapy. The distinction between these two terms is very important as their goals are very different. The objective of the first is solely to acquire new knowledge, while the objective of the second is not only to acquire new knowledge, but also to save a life or improve the health of the
research subject. Usually, an experimental therapy is applied to only one person and must offer the hope of benefiting the health of that person. In contrast, a purely scientific experiment is conducted on a group of people of the same age and with the same disease or handicap, and the expected results must be beneficial to others who possess those same characteristics.2

With regard to the gene therapy research project described in the presented case, it is appropriate to use the term "experimental therapy" because the project has a therapeutic purpose: that is, to treat children suffering from DMD. The goal pursued by the project is not only to acquire knowledge, but also to improve the health and quality of life of these children. The project thus satisfies the criteria applicable to experimental therapy involving children.

Q2. Is it ever acceptable to perform gene therapy research involving children?

According to international and national norms on human research, it is acceptable, in some specific circumstances, to perform gene therapy research involving children. Indeed, the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) require that vulnerable people should not be included in research unless the research is indispensable to the improvement of their health and it cannot be done with people who are capable of providing consent.3,4 The CIOMS goes further by specifying that the participation of children in clinical trials is indispensable for carrying out research into children's diseases (directive 14).

In Canada, the guidelines produced in 1990 by the former Medical Research Council of Canada5 (now the Canadian Institutes of Health Research) were the first to recognize the importance of including children in clinical trials of gene therapy. They indicated that the diseases that lend themselves best to these studies are generally fatal at a very young age. They emphasized that the potential advantages for these children would be greater if the disease were treated before it has caused irreversible harm. (These guidelines were later replaced by the Tri-Council Policy Statement.6) In 1994, the Report of the Royal Commission on New Reproductive Technologies followed the same direction in specifying that people suffering from genetic diseases should be treated from the time the disease is diagnosed in order to maximize the possibility of therapeutic advantages.7 Finally, the Tri-Council Policy Statement (amended in 2005) anticipates that children will not be automatically excluded from research projects that could be beneficial to them due to their legal inability to consent (article 5.3).6 The Tri-Council Policy Statement goes on to say:

"A dilemma exists in that the most likely diseases to be considered for gene alteration are severe, progressive and fatal in childhood (e.g., immune deficiencies). Early treatment for maximal effect means the subject is less able to give free and informed consent because of immaturity. Furthermore, long-term effects are unknown in this age group. However, if research is restricted to those who are able to give consent, many severely affected children would be excluded." (p. 8.6)

Following an analysis of these normative documents, it is possible to conclude that DMD is a disease that lends itself to gene therapy research with children. It is a fatal genetic disease that appears early in life. There is a rapid evolution, so people suffering from it rarely reach the age of majority. Those who do reach 18 years of age are generally in the terminal phase, meaning that the damage is irreversible and treatment may well be ineffective. In addition, if clinical trials on gene therapy are carried out only in those who are capable of consenting, seriously ill children will be excluded from research and the effectiveness of treatment will be extremely compromised due to the evolution of the disease (e.g., muscles too damaged to be treated). It is therefore absolutely essential that research on DMD be undertaken among children with the disease in order to allow them to derive maximum benefit and to improve their quality of life.

Q3. What are the benefits and harms of such research? Are they reasonable?

At the international level, the Declaration of Helsinki states that every research project "must be preceded by careful assessment of predictable risks and burdens... in comparison with foreseeable benefits" (article 18).5 It adds that the research should be stopped when the risks outweigh the potential benefits (article 20). The CIOMS specifies that researchers must ensure equilibrium between the potential risks and benefits of the research and that the risks have been minimized (guideline 8).4 When the intervention offers hope of direct benefits to the research subject, the risks must be justified in light of the expected benefits. When the intervention offers hope of indirect benefits, the risks must be reasonable considering the significance of the knowledge obtained. Moreover, the research subjects cannot be exposed to anything beyond a minimal risk, comparable to that of a routine medical procedure (guideline 9). The CIOMS adds, however, that these risks could be increased if there is an overriding medical reason to do so and approval of a research ethics committee.

In Canada, the Tri-Council Policy Statement indicates that research cannot expose children to a more than minimal
risk unless there is the potential for direct benefits from their participation (article 2.5c). It specifies that the equilibrium between the risks and the advantages resulting from the participation of children suffering from incurable diseases must be the subject of special reflection, but does not provide specific details on this point (articles 2.5 c). This position contrasts with the particular approach taken by the province of Québec. The Civil Code of Québec indicates that children can participate in an experiment when there is an absence of serious risk for their health and when there is a benefit for their health or for the health of other children possessing the same characteristics of age, illness or handicap (article 21). It considerably limits the degree of acceptable risk and does not take into account the proportionality between potential risks and benefits.

In the present case study, the evaluation of risks and benefits might be problematic. Given that the proposed therapy does not currently constitute a proven treatment for DMD in children, the method of evaluating the equilibrium between risks and benefits could vary from one research ethics committee to another. Indeed, some ethics committees might emphasize the possible risks resulting from gene therapy. As mentioned above, these risks are a potential immune system reaction and risk of tumour. These constitute serious risks that could compromise the life of the child and, therefore, may supersede all possible benefits.

However, other ethics committees may take into consideration the fact that these children are confronted with imminent death and that there is no treatment to save or prolong their lives. They could also accord particular attention to the fact that, even if this treatment cannot currently cure these children, it could still improve their quality of life by allowing them some increased mobility. Because it could be the last hope for these children, who have such a short lifespan, some ethics committees might conclude that it is reasonable to allow them to participate in a research project on gene therapy. In the province of Québec, however, because of the particular context raised by article 21 of the Civil Code of Québec, it would be impossible to undertake such a clinical trial with children because an absence of serious risks for their health cannot be demonstrated.

**Q4. Does a child need to assent to his/her participation in the gene therapy research? If a child dissents, should his/her decision be respected?**

Assent comes from the principle of respect for the person and makes it possible for children to exercise autonomy within the limits of their capacity to do so. Thus, including the child in the decision-making process respects his/her developing maturity. Various international norms require the assent of children who are capable of understanding the nature and consequences of the research project in which they have been invited to participate. The child’s assent must be obtained after the consent of the parents or legal representative. When seeking the assent of the child, the researcher must take into account the child’s age and ability to understand what participation in the genetic research project involves. To do this, the researcher should inform the child about the methods and procedures involved in the trial, and about the risks and benefits that may result from participation in the research project. This information should be provided in language appropriate to the age of the child and to his/her level of understanding and stage of development. Like consent, assent is a continuing process that requires renewal over the course of the research project. It must be re-obtained when the research project undergoes significant changes.

When a child expresses refusal to participate in a proposed research project, his/her dissent must be respected unless the decision is harmful to his/her health. However, the parents or legal representative of the child could supersede the child’s refusal in two situations: when the child is too young, too immature or incapable of understanding the research project; or when the research project constitutes the only possible intervention and offers hope of benefit for the child. Thus, the objections raised by the child during the research project should also be considered, and his/her wishes should be respected if this choice is not harmful to his/her health.

In Canada, the Tri-Council Policy Statement emphasizes that even if children cannot express free and informed consent because of their lack of maturity, they can nevertheless “express their wishes in a meaningful way” (article 2.7). It also states that the consent of the parents or legal representative must have been obtained before seeking the assent of the child (article 2.7). Finally, the Tri-Council Policy Statement only specifies that the dissent of the child will exclude him/her from the research (article 2.7).

**References**


Further Reading