Gene therapy

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Findings by Alert

Research in gene therapy has increased dramatically during the past 15 years, particularly in the United States. The research has encompassed the development of gene delivery vectors (carriers) for gene transfer, both viral and non-viral, gene transfer to cells in culture, animal experiments, and clinical trials.

Preliminary results from animal experiments approximately 10 years ago led to the first transfer of a foreign gene to a human in 1989, and to clinical gene therapy trials the following year. Since then, nearly 400 clinical trials have been registered. Studies have yet to show any distinct clinical benefits to patients.

The difficulty in most studies has been an insufficient transfer of genes to the relevant target cells. Hence, it is too early to predict the benefits and potential risks to patients who undergo gene therapy. The effectiveness and potential complications will vary widely depending on the nature of the disease and the transfer method used.

Alert has found there is poor* scientific evidence available on the risks of gene therapy. No* scientific evidence is available concerning patient benefits or the cost effectiveness of gene therapy. Currently, gene therapy should be considered experimental and without specific clinical applications.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

Gene therapy aims at transferring a gene to relevant target cells to correct or improve the function of the defective genes. Gene therapy can also be used to reduce or eliminate disease engendered proteins or proteins that exist in abnormally high volumes (eg, in cancer).

Vectors are used to transfer genes. Many of the best vectors are viral. Viral vectors use components from viruses to draw upon the effective mechanisms which viruses have developed to enter host cells. They then carry a therapeutic gene, but lack one or more viral genes to avoid the complications which may appear when viral genes are present. Most viral vectors lack the ability to reproduce and therefore cannot spread after they transfer their material to the target cells. Some virus vectors can transfer genes permanently by integrating their genetic material into the DNA of the target cells. Other viral vectors do not integrate their genetic material into chromosomal DNA. Particularly in cells which divide, this type of genetic material tends to disappear.

Non-viral vectors also exist. Generally, they are less effective in transferring genes to cells, particularly when it comes to permanent transfer. Recently, researchers have successfully developed more effective methods for transient gene expression.

Gene therapy methods can be divided into ex vivo therapy (treatment outside of the body), where cells from the same species or from the body itself are treated with viral vectors and then returned to the patient, and in vivo therapy where the vectors are injected into the patient directly. Several different approaches using different viral and non-viral vectors, either ex vivo or in vivo, have been tested in clinical trials.

The potentials and limitations of gene therapy deal not only with the development of viral vectors but also with techniques and knowledge in cell biology, eg, the ability to cultivate target cells in appropriate ways without damaging their biological potential. Another requirement is the availability of clinical methodology for injecting viruses into suitable target cells, or in the case of ex vivo therapy, the availability of appropriate transplantation technology. For example, bone marrow transplantation is a well-established medical procedure in contrast to the transfer of liver cells. For blood disorders, it is probable that variants of existing technology may be used in the future, while, eg, liver disorders will require new technology to transfer genes.

Vectors for clinical use are produced in laboratories, specially authorized by Sweden's Medical Products Agency, which adhere to the principles established for pharmaceutical production. A unique situation concerning gene therapy based on viral vector transfer is that the vectors must be analyzed for the presence of infectious viral particles.

Target group

Since gene therapy methods remain experimental at this stage, it is not possible to define specific target groups. Although patients with genetic disorders are viewed as the primary beneficiaries, in recent years other patients groups have also come under study.

Potential candidates for gene therapy include several relatively unusual but serious and difficult-to-treat genetic diseases, eg, Gaucher's disease, hemophilia, cystic fibrosis, and Diamond-Blackfan anemia. In Sweden, for example, there are approximately 40 patients with Gaucher's disease, 200 patients with hemophilia of a type that is so severe it may require gene therapy, and approximately seven patients with Diamond-Blackfan disease.

Other potential areas include cancer, severe infectious diseases (almost exclusively HIV), autoimmune diseases, and degenerative neurologic diseases. The group of genetic diseases includes more than 5 000 disorders, and all disease genes are not yet identified. In recent years, trials have been started to treat cardiovascular disease by stimulating the regeneration of blood vessels. Should these trials be successful, the method could potentially apply to a large number of patients. DNA vaccination is another growing research area, but directed primarily at vaccination for infectious diseases.

Relation to other technology

Currently, no special clinical applications are available for comparative assessment. Successful gene therapy can potentially lead to permanent cure. Most forms of conventional drug therapy for genetic diseases require continuous treatment for the patient's lifetime.

Patient benefits

No definite clinical benefits have been demonstrated in clinical trials.

Complications and side effects

The risks in gene therapy are not well known due to limited clinical experience, but certain complications have appeared in animal experiments, and many potential risks exist. The primary risks observed in animal trials have been immunological. Animals have developed antibodies against the transferred gene or against viral proteins from the vectors used in transfer (particularly adenovirus).

There is also a potential risk for vectors to be integrated in DNA in places where they may have an adverse effect. For example, an oncogene (a gene which causes cancer) could be activated or a gene that inhibits tumor growth could be damaged. The degree of risk is unknown. In animal experiments, the risks have been low, but how low is not known since it would require experiments on thousands or tens of thousands of animals to determine. In comparison, many established forms of therapy for cancer use drugs that influence genetic material and lead to permanent changes. Other risks concern a development of undesired infectious agents in the production virus vectors. Complications that stem from vector production may essentially be prevented through rigorous tests of the vector preparations. Such an analysis is required by the Swedish Medical Products Agency.

Costs and cost-effectiveness

Most gene therapy methods are expensive. DNA vaccination is an exception since viral vectors are not used and they are administered in the same way as conventional vaccines. The costs vary depending on the disease and method used.

Gene therapy of hematopoietic stem cells is expected to cost as much as bone marrow transplantation, excluding the costs for producing and testing the vectors. The costs of vector production can be estimated to reach about 1 to 1.5 million SEK for treating approximately ten patients.

The high cost per patient has been an obstacle in the development of gene therapy. Since gene therapy often focuses on rare diseases, drug companies have shown limited interest since they prefer to focus on common diseases where the development costs per potential patient are lower.

Although few patients would benefit, the savings to society could be substantial if gene therapy is successful. Gaucher's disease is treated, eg, with enzyme replacement at a cost of approximately 60 million SEK per year for approximately 30 patients. Since the patients require life-long treatment the total costs are high. Given an average treatment time of 50 years, and using the current cost for drugs and a 3 per cent discount interest, the lifetime costs would be 52 million SEK. Should the one-time cost for treatment be less than this sum, there would be a savings to health care. In addition, several other humanitarian and socioeconomic consequences should be considered.

Structure and organization of health services

Currently an adequate structure exists to start clinical gene therapy studies on humans. A vector production unit exists at Huddinge University Hospital, and both Huddinge University Hospital and Lund University Hospital have laboratories with the capacity to transfer genetic material to patients. Uppsala University is in the process of developing a production and transfer unit for gene therapy.

Ethical aspects

Somatic gene therapy (gene transplantation) is legally compared to organ transplantation and is basically similar to traditional drug therapy as regards risk assessment. In clinical trials, basic ethical judgment does not differ from other forms of therapy. All information concerning gene transfer vectors (drugs), the medical approach, and the clinical procedures must be assessed. Furthermore, alternative treatments must be considered to assess the risks for patients included in studies. As with all drug treatment, it is important in Sweden to monitor the discussions under way in Europe and EU to develop appropriate guidelines for gene therapy. The Medical Products Agency has evaluated a few applications for conducting clinical trials in Sweden.

Current evaluation research

According to an international database, in June 1999, there were 380 clinical studies registered on gene therapy. Of these, more than 70 per cent were registered in the United States and less than 20 per cent in Europe. In total, at least 3 000 patients are included in these studies. The first clinical gene transfer in Sweden was carried out at Huddinge University Hospital in 1995.

Huddinge University Hospital and Lund University have already established gene therapy centers for developing and supporting gene therapy research. Most Swedish universities have established some form of research in the field, including the following areas: vector development, gene transfer to hematopoietic cells, gene transfer to the central nervous system, and development of cancer gene therapy. A national program for gene therapy research was announced in 1999. In total, 60 million SEK will be invested over a 5-year period.

Experts

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