Bioethical conflicts of gene therapy: a brief critical review

Conflitos bioéticos da terapia gênica: uma breve opinião crítica

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Summary

Methods and techniques employed in gene therapy are reviewed in parallel with pertinent ethical conflicts. Clinical interventions based on gene therapy techniques preferentially use vectors for the transportation of therapeutic genes, however little is known about the potential risks and damages to the patient. Thus, attending carefully to the clinical complications arising as well as to security is essential. Despite the scientific and technological advances, there are still many uncertainties about the side effects of gene therapy. Moreover, there is a need, above all, to understand the principles of bioethics as both science and ethics, in accordance with its socioecological responsibility, in order to prioritize the health and welfare of man and nature, using properly natural resources and technology. Therefore, it is hard to determine objective results and to which extent the insertion of genes can affect the organism, as well as the ethical implications of it.

Keywords: gene transfer techniques, gene therapy, bioethics, ethics, clinical.

Introduction

The first scientific work involving gene transfer was described in 1944 and involved two strains of *Pneumococcus*, one pathogenic and the other nonpathogenic.[1] However, only in the 1950s the three-dimensional structure of DNA was elucidated, allowing the emergence of what we now know as genetic engineering. Since then, the possibility of using the genes or gene fragments for different scientific purposes emerged.[2]

About 10 years later, in 1963, the idea of anticipating the *in vitro* culture of germ cells genetically engineered to obtain direct control of these cells by selecting and integrating specific genes in human chromosomes arises.[3] Since then, numerous experimental designs in order to establish safe methodologies to insert healthy genes into defective cells were initiated.

However, the first successful *in vitro* gene correction in mammalian cells occurred in 1977, using a viral vector as vehicle to transport the genetic material.[4] The first clinical trial of human gene therapy was performed in 1989 using a viral vector in five patients with metastatic melanoma.[5] This pioneering study in humans established a number of important experimental designs for future clinical interventions using gene transfer.

The method stimulated intense research in subsequent decades in an effort to optimize viral vectors for the insertion of therapeutic DNA, leading to the possibility of clinical applications in humans.[6-8] The choice of viral vectors for the purpose occurred because these beings possess the ability to recognize and infiltrate naturally in the cell nucleus, and thus transfer the therapeutic DNA into the host cell.[9]

Moreover, with the advent of human genome sequencing and the development of new software tools for comparing genes, the diagnosis of almost all human diseases related to genetic defects became possible. Thus, gene therapy is currently the most efficient and promising clinical tool available, being capable to predict with a high level of accuracy if someone will develop a disease, as well as to cure it.[10]

In general, gene therapy can be organized according to its cellular target, being called somatic gene therapy when the target is limited to somatic cells.[11] This thera-

peutic method can also be considered an *ex vivo* system, since tissue samples or cells from the patient must be collected for biopsy with subsequent reimplantation after the cells are reprogrammed genetically allowing the correct synthesis of desired gene products.[12] Another widely used method involves germ cell lineages generated after collection; the genes of interest are reprogrammed so that the new features will be perpetuated for future generations of cells from the patient.[13]

From the *ex vivo* application, it was possible to develop a method of *in vivo* gene therapy based on mRNA interference (RNAi). The scientific reports on RNAi date from 1998, initially identified in the nematode *Caenorhabditis elegans*,[14] and, since then, this mechanism has been identified in many species,[15,16] included in all eukaryotic phyla.[17]

The term RNAi refers to a set of small sequences of double-strand RNA (dsRNA), with size from 21 to 28 nucleotides, capable of inhibiting the expression of messenger RNA target sequences with high specificity.[18,19] After the discovery of these molecules, the possibility to use these sequences as a new therapeutic approach, especially for humans, was seen.[20] As such, RNAi-based gene therapy represents today the most advanced form of intervention in genetic diseases among the methods used in gene therapy, with very promising results.[21-23]

Nevertheless, thorough attention must be given to clinical complications arising from the use of gene therapy,[24] as well as to safety certification tests. Human clinical trials based on gene therapy are first carried out in animals and, sometimes, there is not a concrete correlation between the animal models used and the actual human biochemical and physiological conditions.[24]

Despite the scientific and technological advances regarding gene therapy, there are still many uncertainties about the side effects of treatment. Furthermore, the lesser-known effects, such as long-term expression of the introduced genes, the lack of control of the expression of these genes and genetic modification of germ cells, are now ignored.[25] There is no doubt that the main problem to be overcome is currently the high immunogenicity of viral vectors introduced into the patient,[26,27] as well as problems related to efficacy, toxicity and inflammatory response.

Other methods of gene therapy include the injection of genetic material directly into the target tissue,[28] and a variety of natural, synthetic and inorganic nanoparticles, including liposomes, micelles, exosomes, synthetic organic polymers, carbon nanotubes, quantum dots, gold nanoparticles and more, which have been conjugated to nucleic acids and used in gene therapy.[29]

Therefore, the aim of this paper is to present the fundamentals of using gene therapy as a practice of clinical intervention under the scope of bioethics, as well as its implications for the patient.

Bioethical and legal issues of gene therapy

The success of gene therapy led to a boom in the development of several studies with prospects for therapeutic use of genes. And soon after April 14, 2003, the day that the mapping of the human genome was completed, it became possible to diagnose and treat many diseases of genetic origin before they progress,[30] using gene therapy. However, these findings have triggered a series of bioethical controversies about the safety of genetic engineering and the likelihood of its use for the purposes of eugenics.[31]

Gene therapy is a therapeutic strategy characterized by the transfer of genetic material in order to rearrange the genome of target cells to enable expression of the inserted gene or inhibit the expression of a specific gene.[32] Among the methodologies used in gene therapy, there is the application of RNAi, widely used in biomedical research in recent years,[33] due to its relative ease of handling.[23]

Quality of life is a concept that has been extensively studied in recent years, and integrates different fields of knowledge, especially those included in health sciences such as medicine, psychology and biology, and more. In this context, medicine presents itself as a primary mediator in order to prevent diseases and to maintain good health of the patient; science cannot afford to use a still unfinished therapy such as gene therapy at this time, since it is still experimental.

With the advances made in biotechnology in recent decades, the clinical responsibility of medical practitioners and of the debates about intervention methods used by them has inevitably increased. The participation of everyone in order to contribute their views on bioethical issues inherent in aiming at analyzing the risks and expected benefits of gene therapy is indispensable. So, today, to be part of that context and help to guide better decisions, rules of deontological ethics are not enough, and there is the need for plural and interdisciplinary reflections, always focused on human dignity.

Although the advantages of sequencing the human genome have been widely accepted , there are still ethical concerns regarding those benefits,[34] and several problems were encountered in clinical protocols, making it clear that we still have a long way to go before employing technology RNAi in modern medicine.[31]

From the perspective of bioethics, the use of gene therapy appears to be closely related to several negative factors. Among which, can be cited: economic difficulties,[35] particularly with regard to wealth distribution, political and cultural conflicts, as well as the scarcity of studies evaluating the impacts of the use of gene therapy on human health (clinical dilemmas and legal issues).[2, 36, 37]

Some methods, including RNAi, are associated with the use of pathogenic (however attenuated) viruses as transport vectors. The initial proposal for the use of viruses as carriers to transport and introduce genes into a patient seems to be very simple; however, some of them are associated with severe human disease, such as viruses causing pharyngitis, conjunctivitis, leukemia and AIDS. The use of viruses belonging to the lentivirus family, which includes HIV, seems very dangerous, because with the exception of African communities, the global population does not have antibodies against this pathogen.

Overall, gene therapies are new procedures that are still in the experimental stage. This is a very risky therapy, since many vehicles are viruses with genetic material consisting of RNA and, therefore, they can more readily undergo genetic recombination and become more virulent. From the point of view of bioethics, the main obstacle to the application of RNAi-based gene therapy is the fact that the safer non-viral vectors currently available are still inefficient or have very limited application. Therefore, studies that evaluate the effects in experimental models and in preclinical trials are needed in order to validate the potential effectiveness of this type of therapeutic intervention. It is necessary to evaluate the actual benefits as well as to detect the potential risks of implementing this therapy so that both safety and human health are preserved, and worse health problems than those we have today are avoided.

The speed and effectiveness of some of the protocols used in gene therapy have not allowed much scientific and legal discussion about experimental regulation and commercialization, or about the long-term effects of this new therapeutic approach.[38] This decade, it is essential to further understanding about the side effects arising from clinical trials, in order to intervene if necessary. New experimental designs to determine the faults and dangers arising from the use of gene therapy before their deliberation and hence the application as routine technique in hospitals and health centers are, therefore, timely and indispensable.

In 2008, the number of clinical trials using gene therapy as an intervention method reached 118 and since then there has been a decrease in these experiments. Probably be due to temporary restrictions, omitted flaws in the protocols, or even bioethical issues. Over the past four years, clinical trials using gene as a therapeutic mechanism were recorded in more than 33 countries, with representatives from all continents, although the American continent is responsible for over 50% of the trials currently in progress. It is worth saying that the numbers may be underestimated due to the scarcity of information made available and the omission of data in some countries.

The vast majority of clinical trials using gene therapy is currently connected to cancers (64.3%) with a total of 1,223 trials; monogenic hereditary diseases (8.8%) with 1,667 trials; heart disease (8.3%), 158 trials; infectious diseases (8%) with 153 trials; neurological diseases (1.9%) with 36 trials; optical diseases (1.5%) with 28 trials; inflammatory diseases (0.7%) with 13 trials; and other negative factors associated with genetic disorders (6.5%), 119 trials.

In the global legal context, the use of experimental trials with the inclusion of intrinsic parts of animals, plants or other organisms including DNA, RNA and stem cells in humans was always challenged to face dilemmas, insecurity, especially about the consequences of the development of biomedical sciences and biotechnology. This idea is defended in both the international sphere as in the constitution of many countries, in addition to statutory law involving the subject.

In this context, it is vital, above all, to understand the principles of bioethics and ethical science aligned with their socio-ecological responsibility, so as to prioritize the health and welfare of man and nature, in order to properly utilize the natural resources and technology. Among the fundamental principles of bioethics and biolaw are respect for life in all its forms and manifestations, and the quality of the environment, to ensure the maintenance of life and vital processes, with an ongoing commitment to transparency and the dissemination of knowledge involving biological and medical sciences.

The law relating to the use of gene therapy is rarely debated in scientific circles, because of great resistance on the use of these clinical trials, despite numerous prospects for curing different diseases. However, such perspectives are submerged in dubious methods, and the effects of the projects now under study are not predictable. On the one hand, men are entitled to life and health, as stated in the Universal Declaration of Human Rights; on the other hand, there is the question of to what extent we

can risk this right on behalf of still unfinished scientific research.

As in other areas of research, validation of new therapeutic methods is closely related to the development of clinical trials, and prior approval by local, national and international ethics committees is, therefore, required. Some types of vectors, notably adenoviral and retroviral vectors, have produced serious and even fatal side effects and, therefore, security seems to be the main obstacle for the application of this type of clinical intervention in hospitals and other public health care centers particularly in underdeveloped areas or countries.

Not so far from the new technological possibilities applied to modern medicine, many matters involving moral and ethics were raised with heated debate, especially on the behavior of the professionals involved - including doctors, researchers, patients and other people involved with the problems of medicine and public health.

Conclusion

The main difficulties faced by researchers dealing with gene therapy are the following: (1) efficiency during gene transfer, which requires greater effort by researchers in order to optimize vectors that can transfer DNA to target cells as planned; (2) Amplifying and expressing the heterologous gene naturally as seen with resident genes, so that the patient can undertake a single treatment; (3) Minimizing the biological risk caused by viral vectors currently used, adopting more meticulous safety assessments and studies, especially in the case of virulent genes to target cells; (4) Preventing unwanted expression of the heterologous gene or vector, since this may trigger immunological responses in individuals under treatment.

Resumo

Conflitos bioéticos da terapia gênica: uma breve opinião crítica.

Métodos e técnicas empregadas na terapia gênica são revisados em paralelo a conflitos éticos pertinentes. Intervenções clínicas com base em técnicas de terapia gênica são usadas preferencialmente em vetores para o transporte de genes terapêuticos; porém, pouco se sabe sobre os possíveis riscos e danos para o paciente, sendo necessário atender cuidadosamente às complicações clínicas resultantes, bem como à segurança. Apesar dos avanços científicos e tecnológicos relacionados à terapia gênica, ainda há muitas incertezas sobre os efeitos colaterais do uso dessa terapia. Além disso, é necessário, acima de tudo, compreender os princípios da bioética como uma ética da ciência para com a responsabilidade socioecológica, a fim de priorizar a saúde e o bem-estar do homem e da natureza, utilizando adequadamente recursos naturais e tecnologia. Portanto, é difícil afirmar qual é o rendimento real, bem como os resultados do aumento da genética inserida no organismo e as implicações éticas.

Palavras-chave: técnicas de transferência genética; terapia gênica; bioética; ética clínica.

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