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Personalized medicine Related to Gene Therapy, Ethics

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Abstract:
Gene therapy, as an experimental therapy, is applied for the treatment of diseases through modification of genes. Gene therapy corrects the mutated genes. Somatic and germline gene therapy are two main types of gene therapy. In germline editing, normal genes are inserted into the human's eggs or sperm, zygote, or early embryo. Therefore, the gene is transmitted to the next generation, but in somatic gene therapy, a normal gene is inserted into somatic cells and corrects the defective gene without transmission to children. Personalized medicine is a novel therapeutic protocol for the prevention and treatment of diseases that considers individuals' responding differences to medications. So, it raises ethical issues. Ethical concerns regarding gene therapy and personalized medicine are as follows: safety, accessibility, cost-efficiency, genetic enhancement, dignity, autonomy, identity, and social discrimination.

INTRODUCTION

Gene therapy is among new treatments accompanied by modification of genetic material. This modification begins with the insertion of exogenous DNA into patients' cells in order to treat genetic diseases (1). Gene therapy can correct the mutated genes or site–specific changes (2). This treatment is performed using and manipulating vectors for transferring extra genetic material to target cells (2). Delivery vehicles (vectors) are usually viral or non-viral, such as plasmid and non-structured ones (2).

Viral vectors are important in gene therapy for the simple invasion to host and target cells and injection into their genomes (2). Viral vectors include retrovirus, adenovirus, and adeno-associated virus (3).

There are multiple protocols in relation to the application of gene therapy including knocking out or inactivating the mutated gene, insertion of a new gene into target cells, and replacing abnormal genes (4).

New technologies like gene therapy and genetic engineering change organisms' genetic material, but gene therapy prevents or treats genetic disorders through the correction of genetic defect. While genetic engineering leads to an increase in the organisms' abilities by making changes in the genes (5). Since 1990, when gene therapy was presented for the treatment of adenosine deaminase deficiency for the first time , gene transfer protocols have been improved and developed for human use in several diseases like inherited disorders mostly single-gene recessive disorders, such as hemophilia, cystic fibrosis, sickle cell anemia, blindness, etc. as well as cancers and some non-hereditary diseases like diabetes mellitus, Alzheimer's disease and etc. (3, 6).

Now, the use of cationic liposome technology is interesting as one type of non-viral gene transfer approach because cationic liposomes can bind to negatively charged DNA or RNA due to their positive charge and enter target cells.

Also, another non-viral vector, namely naked DNA or RNA can deliver the gene to target cells. Plasmid DNA (pDNA) transfers DNA, cytokine, and other genes to cells, such as T lymphocytes (7).

The development of vector systems in gene therapy at in-vivo and ex-vivo levels of gene insertion leads to treatment of the human diseases using gene transfer. In cancer immunotherapy, chimeric antigen receptor (CAR)-modified is applied to treat blood cancer (8). Genome-editing technology edits genes via the integration of the correct gene to a specific genetic locus. Clustered regularly-interspaced short palindromic repeat (CRISPR)–associated systems (CRISPR–Cas), transcription activator-like effector nucleases (TALENs), and zinc finger nucleases (ZFNs) change a DNA sequence via a double-strand break to correct a modified gene. However, these tools should be used safely and effectively (8). An important ethical question is about embryo editing by editing germline mutation (8). Researchers face some challenges regarding successful gene therapy like identification of faulty genes and specific cells underlying treatment, the problem of gene transfer, different vectors with

different efficiency, and ethical issues about somatic and germline gene therapy (9).

Somatic and germline gene therapy are two main types of gene therapy. In somatic gene therapy, gene is inserted into somatic cells to correct abnormal genes of cells. This approach is usually successful and abnormal genes are not inherited by the next generation, but germline gene therapy modifies genes in sperm or ova germline cells, which are inherited by the next generation (10).

Stem cells can reproduce and differentiate into specialized cells including embryonic and adult stem cells (11). Pluripotent embryonic stem cells can produce more than 200 different cells leading to differentiation of three germ cell layers, namely endoderm, mesoderm, and ectoderm (12, 13). Pluripotency of stem cells and their unlimited reproduction has made them be used in regenerative medicine (12). Plasticity of stem cells is referred to the differentiation level to numerous cell and tissue types. Plasticity varies from unipotency to totipotency (12). The aim of stem cell therapy is in line with regenerative medicine because both treatments restore and recover the impaired cells (14). Totipotent cells or blastomeres can generate a whole new organism but pluripotent cells can produce 200 types of tissue. Also, mesenchymal stem cells can generate a small variety of multipotent tissues. When stem cells produce one lineage, it is unipotent. Human gonads involve stem cells called as spermatogonia and oogonia having the potential to produce germ line cells, spermatozoa, and oocytes. Adult stem cells are differentiated cells and can de-differentiate and partially repair injuries of a specific organ (12). Compared to embryonic stem cells, adult stem cells are applied extensively in clinics to generate various cell types and regenerate, repair, and treat organs, such as the heart, as well as cancer and systemic diseases. Mesenchymal stem cells have the capacity to differentiate into many cell types like chondroblasts, osteoblasts, osteoclasts, and other cell types (15). It is hoped that cardiomyocytes can differentiate to the myocardium and promote cardiac function. Humanś myocardium can consist of cardiac myocytes after transplantation into animals.

Embryonic stem cells can reconstruct impaired tissues or cells or change humanś organs because they can construct any cell, tissue, or fetus. Argumentative issues on research about embryonic stem cells are raised because these experiments can lead the loss of humanś embryos. Human cloning and stem cell investigations have negative consequences for gene therapy (16).

There is an important controversy related to gene therapy among scientists about fears associated with gene technology, modified nature, and ethical issues (17). Attention to gene therapy risk, risk acceptability, and side effects of this trial has opened a new light to the use of gene therapy as a safe and proper treatment for patients (10).

The aim of gene editing ethics determines the ethical implications of using gene modification in somatic or germline cells. Germline gene therapy has been considered as a controversial issue in medicine and science centers such as the national academy of sciences (NAS) and Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations". Unintended modification of germ cells from an ethical viewpoint especially in-vivo gene therapy should not be confused genetically (18). Ex-vivo manipulations in genome editing of embryos lead to spontaneous germline alterations and their risks. There are some ethical issues about germline gene therapy, such as practical limitation, lack of achievement in pre-implantation stage of genetic diagnosis ، inefficiency of the current procedures of zygote editing, and lack of efficient procedure for evaluation of the modified germ cell and long-term outcome, such as cancer or developmental side effects (18). Gene therapy is useful for treatment of the patients with a genetic disease or those who have developed cancer and gives a chance to them to live normally. Also, gene editing leads to stable and long-term expression of protein, insertion into right site, and targeting specific cell. In spite of usefulness of this approach, it has disadvantages, such as the lack of proper genetic tests to detect the mutated gene in order to replace it with normal gene, pathogenicity of vectors, immune response against this protocol, and ethical concerns (9).

Transferring genes to the somatic cells is performed in three ways namely, in-situ, in-vivo, and ex -vivo.

Gene is inserted directly into the body in-vivo. When the modified gene is introduced into patients' cells out of the body and is replaced back to the patient's body, it is called ex-vivo gene transfer (19).

In germline gene therapy, normal genes are inserted into a human‘s eggs or sperm, zygote, or early embryo. This procedure causes modification of genetic inheritance and leads to an increase in the genetic variation or treats genetic disease. The value and accessibility of this treatment protocol are not known. However, parents prefer to select the desired embryos based on their genetic variations via pre-implantation genetic diagnosis. Somatic gene therapy is the most important barrier to germline gene therapy (20).

Somatic Cell Gene Therapy, Ethical and Social Concerns

Bioethics mainly focuses on genetic engineering. Gene therapy for the treatment of human diseases has resulted in public debate. It both brings about new and worst fears in genetics including the questions raised about" playing God". Many people believe that somatic cell gene therapy is a proper therapy because it provides new sights to produce medications with a low cost (19). Safety and efficacy are very important in somatic cell gene technology when it comes to ethical concerns and should be addressed in the production of drugs and devices, the right selection of patients for the clinical trial, treatment security, protection of privacy, and confidentiality of medical information, and the voluntary option of the procedure must be explained to patients (21).

Germline Gene Therapy and Ethical Issues

There is a debate on germline gene therapy because offspring or the next generation inherits the modified

and transferred genes introduced into sperm or eggs. There is a big question about this intervention, whether a new type of eugenics or genetic enhancement is in germline gene therapy, or whether genetic manipulation in the genetic material of the unborn baby can be acceptable.

Also, there is another debate about the application of germline gene therapy in medicine exclusively or its other application in genetic enhancement, which is the production of the new human being (22). The strong effect of germline gene therapy on future generations, has caused its use to be forbidden in most countries.

There are some complex interactions between human evolution, and social and cultural considerations leading to designing responsible programs for germline gene therapy (23). Two proofs should be considered for this treatment: ethics and safety. The use of ribozymes, RNA-DNA hybrids, etc. is useful for in-vitro fertilization and improves intelligence traits, or contributes to generating the "designer baby" (24). Also, when germline editing eliminates genetic mutation, it can cause harm to the next generation (25). This ethical difference raises the major questions:

Do we have enough information about the effects of long-term treatment, benefits or harms, and side effects?

What is our task regarding the rights, health, chances, and options of the future generation? (25).

Personalized Medicine

Personalized medicine is a novel therapeutic protocol for the prevention and treatment of diseases that considers individuals' responding differences to medications. Personalized medicine advancement resulted in tailored, potent, and proven treatments for specific features of persons, like an individual's genetic makeup, or the genetic profile of an individual's cancer. One of the most personalized medicine is autologous cell therapies in which the patient's own cells are transplanted to the patient. Personalized medicine is a tailored approach based on the right patient, the right treatment, the right dose, and the right time (26).

Today, it was known that patients who have similar symptoms may have different diseases and respond differently to drugs. Discovering and using of conventional treatment for diseases like cancer proper to the patients' features are the main aim of personalized medicine (27).

Recently, patients with genetic diseases like cystic fibrosis and Duchenne muscular dystrophy can be treated by new drugs. These medications targeted specific genetic variants, but these medications gave a better quality of life to the patients. However, individualized cancer drugs have been designed for patients with particular genetic mutations (27).

Also, the term individualized medicine, according to the National Cancer Institute defines information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. Personalized medicine uses from analysis of genomic data for the prediction, prevention, and treatment of human disorders. Genomic medicine or precision medicine is also recognized as personalized medicine. Today, small- and large-scale genomic databases apply in the healthcare system in numerous countries such as the UK (28).

Using of progresses in genomic techniques has caused the marketing of innovative diagnostic approaches for the investigation about therapeutic outcomes in patients. The deep belief of personalized medicine is that the molecular, physiological, and behavioral characteristics of persons are unique. So, they must take tailored drugs and therapeutic approaches. Recently, tests such as genome sequences and genome- wide analyses applying microarray and next- generation sequences determine DNA sequence variants related to common diseases for individual condition risk estimation, and treatment. Direct-to-consumer (DTC) DNA testing presents valuable information about personal genetic make-up such as single nucleotide polymorphisms (SNPs) directly to the users (29).

Personalized Medicine and Medications

The effectiveness of medications with slightly side effects can be increased by genetics. So, the personalized protocol uses genetic factors to be familiar with the patient's information about responding to a drug as "pharmacogenomics". Pharmacogenomics designs new efficient, safe drugs with proper doses based on a patient's genetic material (30).

One of important field of personalized medicine is pharmacogenomics. Numerous factors such as genomics, epigenomics, the patient's features including gender, ag, and the environment effect on interindividual variability to medication response (31).

Analysis of the drug-target network shows that more presently applied drugs include numerous targets and off-target effects. Sequencing, epigenomic profiling and metabolomics as Genome –wide approaches will be needed for recognize the molecular structure of disease etiology and medication response. Genome-wide studies (GWAS) involved novel biological pathways, but this protocol has drawbacks because many variants with clinical phenotypes like dug side effects are not causative (31).

Ethical Issues

Gene modification for therapeutic goals raises ethical concepts because new treatments, such as gene therapy have risks in spite of great benefits for patients cure. Principles of autonomy, dignity, identity, beneficence, and non-maleficence, which are essential for medical ethics, may be controversial. Cloning and germline gene editing are important regarding ethical concepts. Also, eugenic objects and genetic enhancements improving the traits like height and intelligence could be used for treatment of fetal diseases. Moreover, gender selection, embryo chimerization, psychosocial irregularity of the manipulated human, and genetic disassociation have been discussed in relation to ethical issues (32, 33). Prevention of disability and weakened human growth in every society has been considered notably during the last century. Screening, prenatal diagnosis ,pre-implantation genetic diagnosis

(PGD) ,and assisted reproduction techniques (ART) have induced a new constitution proportional to new demands in society but moral and ethical issues about using these procedures have not been addressed (33). Also, there is a debate about designing experimental embryos, choosing embryos ,collection of the cryopreserved embryos , identity, dignity ,and benefits, and new technologies like mitochondrial restoration, human cloning, genomic map change, and CRISP/ Cas9 are controversial (33).

Mechanisms of genome editing directly specify DNA sequences via the modified proteins or RNA-protein complexes for specific genes or non-coding region and produce DNA breaks as single or double strand. For instance, a Cas9 protein with CRISPR ‘‘guide RNA can cut DNA strands at specific site leading to editing the mutated or defective gene. Genome editing is one of easy and available tools but it needs to be approved with respect to ethical issues before large-scale application (34).

A policy was established for ethical standards including gene therapy in 1996 by the American society of gene and cell therapy (ASGCT). So, for protection of patients in gene editing therapy, the food and drug administration (FDA) and national institutes of health (NIH) have explained two actions: Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia (32).

The ethics of personalized medicine

The ethics of personalized medicine is very important issue because the results of some laboratory tests about a high risk of breast or ovarian cancer estimation in women are incorrect, but they did not expose a risk of cancer. Ethical issues are not restrict to using of genetic information, but can increase acquiring of genetic make up for the addition of science and knowledge (35)

Personalized medicine face to some particular legal and ethical challenges such as data gathering, informed consent, distribution and utility, privacy and popular confidence, and altering situation of patients and social equality. So, it is essential to provide the proper balance between scientific and commercial profits, public health and person rights. Also, the legal and ethical perspectives of gene editing technologies such as germline gene therapy should be analyze and interpret correctly (28).

The Big Question: Future of Gene Therapy and Personalized Medicine

So, finding gene /genes of each disease is important in gene therapy. Genome project has opened new sights to new protocols for diagnosis, treatment, and prevention of diseases.

Likely in the future, chance of treating many human diseases will be increased via gene therapy and it is possible to cure the unborn baby with a genetic disorder (36). However, ethical concepts must be considered in gene therapy along with its consequences.

Personalized or precision face to numerous of challenges by using the persons’ genetic make-up. Because genetically –targeted therapies are pricy and troublesome. The cost of personalized genetic tests and drugs for the determination of different persons’ response to medication are not guarantee. All patients must achieve personalized medicine advances without discrimination and abusing (37).

Since using of sequencing technology becomes usual, information about the molecular mechanism and the genetic background of diseases increases and translates into the as higher data, novel treatment and enhanced chances for programming individualized care and health progression (2).

CONCLUSION

In addition to advantages, gene therapy has also some disadvantages. Gene therapy can cure all the diseases, prevent transmission of abnormal genes to the next generation, and help parents to have healthy children .Although, this therapy can have unknown long-term effects or clinical risks, it can improve human traits, such as height and intelligence without disease and select the desired babies or “designer baby” that may lead to social discrimination. Also, this technology is very expensive and is not cost-efficient.

Many ethical issues are very important in gene therapy and cell therapy field with personalized medicine applications because these approaches lead to changes in humans’ genetic material. Ethical concerns must be considered about determining normal and abnormal genes, cost and accessibility for every patient, social discrimination, clinical risks, toxicity, and cancer.

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Consent for publication

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Not applicable

Competing interests

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PP made the conception of the study. PP wrote the main manuscript and revised the manuscript. The author approved the final version.

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REFERENCES:

1.Worgall S, Crystal RG. Chapter 34 - Gene Therapy. In: Lanza R, Langer R, Vacanti J, editors. Principles of Tissue Engineering (Fourth Edition). Boston: Academic Press; 2014. p. 657-86.

2.Gonçalves GAR, Paiva RMA. Gene therapy: advances, challenges and perspectives. Einstein (Sao Paulo, Brazil). 2017;15(3):369-75.

3.Misra S. Human gene therapy: a brief overview of the genetic revolution. The Journal of the Association of Physicians of India. 2013;61(2):127-33.

4.Human Genome Editing: Science, Ethics, and Governance. Washington DC: 2017 by the National Academy of Sciences; 2017.
5.Delhove J, Osenk I, Prichard I, Donnelley M. Public Acceptability of Gene Therapy and Gene Editing for Human Use: A Systematic Review. Human gene therapy. 2020;31(1-2):20-46.
6.Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. Science (New York, NY). 2018;359(6372).
7.Keeler A, ElMallah M, Flotte T. Gene Therapy 2017: Progress and Future Directions. Clinical and Translational Science. 2017;10(4):242-8.
8.Kumar SR, Markusic DM, Biswas M, High KA, Herzog RW. Clinical development of gene therapy: results and lessons from recent successes. Molecular therapy Methods & clinical development. 2016;3:16034.
9.Kumar A, Sharma P, Bhandari A. Gene Therapy: An Updated Review. European Journal of Biotechnology and Bioscience. 2014;1(3):42-53.
10.Goswami R, Subramanian G, Silayeva L, Newkirk I, Doctor D, Chawla K, et al. Gene Therapy Leaves a Vicious Cycle. Frontiers in oncology. 2019;9:297.
11.Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Research & Therapy. 2019;10(1):68.
12.Alenzi F, Lotfy M, Tamimi W, Wyse R. Review: Stem Cells and Gene Therapy. Laboratory hematology : official publication of the International Society for Laboratory Hematology. 2010;16:53-73.
13.Biehl JK, Russell B. Introduction to stem cell therapy. J Cardiovasc Nurs. 2009;24(2):98-105.
14.Muñoz Ruiz M, Regueiro JR. New Tools in Regenerative Medicine: Gene Therapy. In: López-Larrea C, López-Vázquez A, Suárez-Álvarez B, editors. Stem Cell Transplantation. New York, NY: Springer US; 2012. p. 254-75.
15.Gaipov A, Myngbay A. Stem Cells Therapy in General Medicine. European Journal of General Medicine. 2018;15:50-3.
16.Resnik DB. Bioethics of Gene Therapy. eLS(2012).
17.Deakin CT, Alexander IE, Kerridge I. Accepting risk in clinical research: is the gene therapy field becoming too risk-averse? Mol Ther. 2009;17(11):1842-8.
18.Kohn DB, Porteus MH, Scharenberg AM. Ethical and regulatory aspects of genome editing. Blood. 2016;127(21):2553-60.
19.McFarland TJ, Stout JT. CHAPTER 41 - Ocular gene therapy. In: Nguyen QD, Rodrigues EB, Farah ME, Mieler WF, editors. Retinal Pharmacotherapy. Edinburgh: W.B. Saunders; 2010. p. 285-91.
20.Greely HT. Ethical Issues in the 'New' Genetics. In: Smelser NJ, Baltes PB, editors. International Encyclopedia of the Social & Behavioral Sciences. Oxford: Pergamon; 2001. p. 4762-70.
21.Sade RM, Khushf G. Gene therapy: ethical and social issues. Journal of the South Carolina Medical Association (1975). 1998;94(9):406-10.
22.Thiele F. Bioethics: Examples from the Life Sciences. In: Smelser NJ, Baltes PB, editors. International Encyclopedia of the Social & Behavioral Sciences. Oxford: Pergamon; 2001. p. 1190-5.
23.Skorecki K, Galun E. 43 - Cell and Gene Therapy. In: Goldman L, Schafer AI, editors. Goldman's Cecil Medicine (Twenty Fourth Edition). Philadelphia: W.B. Saunders; 2012. p. 203-11.
24.Verma IM. Germline Gene Therapy: Yes or No? Molecular Therapy. 2001;4(1):1.
25.Häyry M. Genetic Engineering of Human Beings. In: Chadwick R, editor. Encyclopedia of Applied Ethics (Second Edition). San Diego: Academic Press; 2012. p. 436-44.
26.Marshall D, Sharpe M, Ward S. Cell & gene therapies and the evolving role of personalized medicine. Cell and Gene Therapy Insights. 2016;2:277-86.
27.Swinney DC, Xia S. The discovery of medicines for rare diseases. Future Med Chem. 2014;6(9):987-1002.
28.Personalized medicine : legal and ethical challenges. 2020.
29.Noori-Daloii MR, Zafari N. The personalized medicine: today and tomorrow. MEDICAL SCIENCES JOURNAL. 2019;29(1):1-17.
30.Ventola CL. The role of pharmacogenomic biomarkers in predicting and improving drug response: part 2: challenges impeding clinical implementation. P t. 2013;38(10):624-7.
31.Schwab M, Schaeffeler E. Pharmacogenomics: a key component of personalized therapy. Genome Med. 2012;4(11):93.
32.Kiwanuka E, Hackl F, Nowinski D, Eriksson E. 15 - Molecular and gene therapies for wound repair. In: Farrar D, editor. Advanced Wound Repair Therapies: Woodhead Publishing; 2011. p. 395-415.
33.Macpherson I, Roqué MV, Segarra I. Ethical Challenges of Germline Genetic Enhancement. Frontiers in Genetics. 2019;10(767).
34.Khan SH. Genome-Editing Technologies: Concept, Pros, and Cons of Various Genome-Editing Techniques and Bioethical Concerns for Clinical Application. Molecular therapy Nucleic acids. 2019;16:326-34.
35.Kushner J. The ethics of personalized medicine. Personalized Medicine Universe. 2014;3:42-5.
36.Patil S, Al-Zoubi IA, Raghuram PH, Misra N, Yadav N, Alam M. Gene therapy: A comprehensive review. International Medical Journal. 2018;25:361-4.
37.Cordeiro JV. Ethical and legal challenges of personalized medicine: Paradigmatic examples of research, prevention, diagnosis and treatment. Revista Portuguesa de Saúde Pública. 2014;32(2):164-80.