Review Paper:

Gene Therapy in India: Current Landscape and Future Prospects

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Abstract

Gene therapy has emerged as a revolutionary approach in the field of medicine, offering potential cures for genetic disorders and other diseases. This review provides an overview of the current status of gene therapy in India, highlighting recent advancements and future prospects. The study encompasses key developments, regulatory frameworks and promising clinical trials, shedding light on India's role in the global gene therapy landscape. The regulatory oversight, primarily administered by the Central Drugs Standard Control Organization (CDSCO), plays a crucial role in ensuring the safety and efficacy of gene therapy products. The document explores the challenges and opportunities associated with the import of gene therapy products into India.

Gene therapy is not approved in India yet and only around ten gene therapies are in clinical trials. As research progresses in this exciting field, it is likely that these therapies will become first-line treatments and will have tremendous positive impacts on the lives of patients with genetic disorders.

Keywords: Gene Therapy, Genetic disease, Clinical Trials, Imports.

Introduction

Gene therapy involves precisely modifying the human genome to induce therapeutic effects in conditions linked to genetic factors.[1,5] To restore the normal function of proteins, these modifications involve the substitution and alteration of faulty genes or even adding functional copies of the genes to cells.[16] To enhance or modify the operation of the target cell, two fundamental approaches have arisen: *ex vivo* and *in vivo* gene delivery.

In the previous three decades, there have been notable developments in the field of gene therapy, despite notable setbacks in its early stages. These difficulties included a leukemia case resulting from insertional oncogenesis induced by a retroviral vector in a clinical trial for severe combined immunodeficiency and a death ascribed to an acute immune response to an adenovirus vector in a trial for ornithine transcarbamylase.[7,20]

Types of gene therapy

There are two categories into which gene therapy falls.

Germline gene therapy: Germline gene therapy is a type of genetic engineering that involves modifying the DNA of germ cells which are the cells that give rise to eggs and sperm.

Somatic gene therapy: Somatic gene therapy is a kind of genetic modification that involves the introduction, elimination, or change of genetic material within the cells of an individual's body, excluding the germ cells (sperm and egg cells).[16]

***In vivo* Somatic Gene Therapy:** "*In vivo*" means "within the living." In *in vivo* somatic gene therapy, the therapeutic genes are directly introduced into the target tissues or cells inside the living organism.

***Ex vivo* Somatic Gene Therapy:** "*Ex vivo*" means "outside the living." In *ex vivo* somatic gene therapy, the therapeutic genes are introduced into cells outside the patient's body before being returned to the patient. [9]

Vectors used in gene therapy: Various methods exist for delivering materials in gene therapy and gene repair, involving viral and non-viral vectors all of which have distinct safety and efficacy characteristics. Adenoviruses, adeno-associated viruses, retroviruses and lentiviruses are widely utilized viral vectors. When choosing a viral vector, various factors must be considered including tissue tropism, the choice between integrating or episomal vectors, immunogenicity, host immunity and the gene size that will be delivered.[4]

Various nonviral vectors for delivering genetic products have been extensively tested and are undergoing evaluation as potential safe and efficient alternatives to viral vectors. Nonviral vector examples encompass liposomes, nanoparticles, magnetofection, electroporation, gene guns, hydrodynamic pressure, sonoporation and cell-penetrating peptides.[12,21]

Genetic disorders in India

These conditions, which affect both physical and mental health, are caused by anomalies in a person's DNA and can take many different forms. In this case, gene therapy is the sole treatment for a hereditary condition.

Cancer: Research on gene therapy and its therapeutic applications has benefited most the field of cancer. By the end of 2021, cancer accounted for over two-thirds of gene therapy research. The goal of gene therapy is to specifically

target and alter the genes that are involved in the growth and spread of cancer cells. This could involve tactics like adding genes that inhibit tumor growth, enhancing the immune system's ability to recognize and destroy cancer cells, or specifically focusing on and eliminating cancer cells.[17]

It was determined that 14,61,000 incident reports of cancer (crude rate: 100 per 100,000) would occur in India in 2022. In India, around one in ten individuals will face cancer within their lifetimes. Lung and breast cancers were the most frequent cancers in men and women respectively. The most common malignancy in children (0–14 years old) was lymphoid leukemia which affected boys 29.2% and girls 24.2%. According to estimates, the number of cancer cases will rise by 12.8% in 2025 compared to 2020.[10]

Down syndrome: A person with down syndrome carries an additional half or complete copy of chromosome 21. Although the cause of this syndrome is currently unknown, down syndrome has always existed and is a part of the human experience.

It is widespread around the world and frequently has varying consequences for physical attributes, learning styles and overall health.[19]

Three distinct forms of down syndrome have been recognized by scientists:

1. Trisomy 21: This happens when there is a cell division defect known as "nondisjunction" which causes an embryo to have three chromosomes rather than two.

2. Mosaicism: This happens when two different cell types coexist—some having 47 chromosomes and others with 46. The additional 21 chromosomes are present in those with 47.

3. Translocation: This kind is somewhat uncommon. In this case, there are still 46 chromosomes, but a partial or extra copy of one chromosome joins forces with another chromosome.

Every year, between 23,000 and 29,000 babies born in India are affected by down syndrome. In India, chromosomal abnormalities are present in about 1 in 166 births, with down syndrome accounting for 1 in 830 cases.[8]

Sickle-cell anaemia: A frequent genetic ailment caused by the inheritance of mutant hemoglobin genes from both parents is sickle-cell anemia, sometimes referred to as sickle-cell disorder or sickle-cell sickness. These hemoglobinopathies are common throughout the world and primarily cause thalassemia and sickle-cell anemia. The hemoglobinopathies-causing genes are present in about 5% of the world's population.[14]

India has the second-most number of SDC reports worldwide (approximately 21 million). A startling proportion of those are kids. In India, between 150,000 and 200,000 newborns are diagnosed with sickle cell disease every year. These infants can expect to live shorter lives and have anemia, organ damage, persistent pain, increased susceptibility to infections and stroke. Fifty to eighty percent of children with sickle cell disease (SCD) never reach five years old.[15]

Tay-Sachs: Tay-Sachs disorder is an uncommon genetic metabolic disorder that primarily affects young children. It is characterized by a progressive loss of brain-related cells. It is brought on by a mutation in the hexosaminidase A enzyme, which permits the dangerous accumulation of lipid-fatty substances like oils and acid in cells. To have a child with Tay-Sachs disease, both parents must have the defective gene. The GM2 gangliosidoses are a class of hereditary illnesses that include Tay-Sachs disorder.[18]

- Infantile Tay-Sachs disorder
- Juvenile (subacute) Tay-Sachs disorder
- Late-onset Tay-Sachs disorder

Hemophilia: Hemophilia is a bleeding disorder that is typically inherited and causes problems with blood clotting. Both spontaneous bleeding and bleeding after surgery or injuries may result from this. Many proteins known as clotting factors are found in blood and can aid in halting bleeding. Low amounts of either factor VIII (8) or factor IX (9) are seen in people with hemophilia.[3] Hemophilia A and hemophilia B disorders occur in approximately 0.9 and 0.1 out of 10,000 people respectively in India.

Cystic fibrosis: The genetic disease cystic fibrosis is caused by mutations in the transmembrane conductance regulator (CFTR) gene. The CFTR protein is made according to instructions from the CFTR gene. Individuals with cystic fibrosis inherit a defective CFTR gene in two copies, one from each biological parent. A CFTR protein that is not functioning properly, is produced by the body when two CFTR genes are altered. The prevalence of cystic fibrosis disorders in India is estimated to be 0.40 percent.[2]

G6PD deficiency: G6PD deficiency is a genetic disorder. It happens when there is a deficit in the enzyme known as glucose-6-phosphate dehydrogenase, or G6PD in the body. Red blood cells require this enzyme to function properly. Hemolytic anemia may result from a deficiency in this enzyme. At this point, red blood cells are oxidizing more quickly than they are being produced. The study covered 72 indigenous groups spread throughout 56 districts across 16 States and two Indian Union Territories. There was a range of 2.3 to 27.0 percent for G6PD insufficiency, with an overall frequency of 7.7 percent.[11]

Clinical trials of gene therapy in India

Gene therapy products have not been approved in India yet and only around ten gene therapies are in clinical trials.[13]

S.N.	CTRI No.	Title	Centre	Date of Permission
1.	CTRI/2022/04/041823	Phase IIa exploratory studies to assess the effectiveness of the "next generation" TGF-β2- selective antisense oligonucleotide ISTH0036 in patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) who have either previously received treatment or are treatment naïve and have severe Nonproliferative (NPDRP) and mild proliferative diabetic retinopathy (PDRP).	Ahmadabad, Gujarat, India.	12/04/2022
2.	CTRI/2022/03/041304	High expression of the Factor VIII transgene in autologous hematopoietic stem cells (CD68-ET3-LV-CD34+) is a gene therapy product for hemophilia A.	Vellore, Tamil Nadu-632002, India	23/03/2022
3.	CTRI/2022/03/041162	A phase 2 trial to evaluate the safety and effectiveness of IMN003A cell treatment for individuals with CD19-positive B-cell malignancies that have relapsed and are refractory.	Bengaluru	16/03/2022
4.	CTRI/2022/03/041060	Phase 1 open-label trial evaluating the safety, tolerability and effectiveness of 2'-O-methyl phosphorothioate anti-sense oligoribonucleotides for the treatment of juvenile patients with confirmed Duchenne muscular dystrophy from India.	Kolkata, India	14/03/2022
5.	CTRI/2021/05/033348	A first-in-human pilot feasibility study investigating the potential of locally produced Novel Humanized CD19-directed Chimeric Antigen Receptor (CAR)-1 (NH19CAR-1) modified T-cells for the treatment of relapsed or resistant B-cell acute lymphoblastic leukemia.	Navi Mumbai, Mumbai-400012	04/05/2021
6.	CTRI/2021/04/032727	A pilot trial involving adult patients with relapsed or refractory diffuse large B-cell lymphoma examined the effects of locally produced HCAR19 (2nd generation anti-CD19-41BBCD3 chimeric antigen receptor T-cell therapy).	Navi Mumbai, Mumbai-400012	12/04/2021
7.	CTRI/2021/11/03/7956	A randomized, double-blind, sham-controlled trial to assess the safety and effectiveness of intrathecal (IT) OAV101 in individuals with later-onset Type 2 spinal muscular atrophy (SMA) who are ≥ 2 to < 18 years old, sedentary and never mobile.	Bandra (East), Mumbai	11/11/2021
8.	CTRI/2020/08/027334	ILLUMINATE-C: A Single Arm Investigation to Assess Lumasiran's (siRNA) Safety, Pharmacokinetics and Pharmacodynamics in Patients with Advanced Primary Hyperoxaluria Type 1 (PH1).	New Delhi	24/08/2020
9.	CTRI/2021/04/032498	A clinical experiment with boys suffering from Duchenne muscular dystrophy to examine the effects of antisense oligonucleotide.	Bangalore	01/04/2021

10.	CTRI/2019/09/021329	Stage 2 of a multi-stage project investigating the potential of locally produced Chimeric Antigen Receptor (CAR)-modified T-cells in the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia that is not eligible for stem cell transplantation.	Navi Mumbai, Mumbai-400012	19/09/2019

Import of gene therapy products in India

Gene therapy is not approved in India yet, So currently, India imports gene therapy products from other countries. Gene therapy products typically require regulatory approval from the CDSCO before they can be imported and used in India. This involves submitting detailed documentation on the product's quality, safety and efficacy. Importers may need to obtain an import license from the CDSCO.[6]

Conclusion

In conclusion, the landscape of gene therapy in India is evolving, with ongoing clinical trials and increasing interest in this innovative field. Gene therapy is not approved in India yet and only around ten gene therapies are in clinical trials. The country has witnessed notable progress in the regulatory framework and infrastructure to support gene therapy research and development. While challenges persist including ethical considerations and the need for further investment, the future prospects for gene therapy in India appear promising.

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