Asian Journal of Pediatric Research

Volume 14, Issue 9, Page 1-9, 2024; Article no.AJPR.122475
ISSN: 2582-2950

Genetic Treatment Approaches in Rare Pediatric Diseases

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2024/v14i9382

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/122475

Review Article

Received: 20/06/2024
Accepted: 23/08/2024
Published: 26/08/2024

ABSTRACT

Gene and cell therapies have been developed and approved for a growing number of pediatric diseases, with ongoing research for additional treatments. Each therapy is tailored to the specific disease and targets a specific genetic alteration or cell population. The development of new therapies is a complex and regulated process, with strict oversight at regional and European levels. Research begins in the laboratory and progresses through clinical trials to ensure safety and efficacy. Scientists are exploring novel therapies using human cells and tissues to model pediatric diseases. Clinical trials are conducted to evaluate the effectiveness of these therapies, and researchers are also investigating repurposing approved treatments for other diseases or aspects of the same disease.

Keywords: Gene therapy; gene addition; gene silencing; gene editing; pediatrics; child.

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Cite as: *Bittmann, Stefan. 2024. "Genetic Treatment Approaches in Rare Pediatric Diseases". Asian Journal of Pediatric Research 14 (9):1-9. https://doi.org/10.9734/ajpr/2024/v14i9382.*

1. INTRODUCTION

Gene Therapy involves using genetic material to treat or prevent diseases. Three common effects of gene therapies in cells include *gene addition*, whereas it is a process introducing a functional gene that contains instructions for the cell to produce a specific protein. Vectors, often viruses, are utilized to deliver the functional gene to the cell's nucleus, where the DNA is housed. The introduced gene may reside in the nucleus permanently after a single administration. Depending on the design, the new gene may integrate into the main DNA or remain adjacent to it, providing additional instructions.

Gene silencing is an approach, where the delivered genetic material hinders or suppresses the activity of an existing gene in a cell, leading to a reduction in the production of a particular protein. A third variant, *gene editing*, is a technique, which involves correcting segments of DNA by modifying or deleting information within an individual's affected gene. Genetic material is directly delivered to edit or alter specific DNA segments within a cell to rectify the protein production. Gene editing employs precise technology to make these targeted modifications. There are many more gene therapies mentioned in the manuscript and especially found in Table 1.

2. DIFFERENT GENE THERAPY APPROACHES

2.1 Gene Additive Methods

Gene-addition tools involve the direct introduction of a functional gene, also known as a therapeutic gene or transgene, into the nucleus of target cells using a vector as a delivery vehicle. When adding a new gene, viral-based vectors are commonly used, either delivered ex vivo or in vivo. Vectors play a crucial role in gene addition techniques. Viruses are utilized as vectors due to their efficient cell entry capabilities, with various types of viral vectors employed for gene addition. Before transporting a transgene into a patient's cells, the vectors are modified to eliminate viral disease-causing genes and their replication ability. After a vector delivers the transgene into the nucleus, where DNA is housed in chromosomes, the cell initiates the production of new proteins to enhance functionality. The gene can either persist as an additional DNA segment in the cell or integrate into the chromosomes and become part of the cell's DNA, both leading to functional protein synthesis.

2.2 Gene Silencing Approaches

Gene silencing is a natural process in genetics where gene expression is suppressed, either by inhibiting transcription or translation of genetic information. Transcriptional gene silencing may involve epigenetic changes to DNA or the binding of repressors to a silencer. Post-transcriptional gene silencing involves processes that occur after transcription of genetic information.

2.3 Gene Editing Therapy

Gene editing aims to modify genetic material directly within a cell by delivering genetic material that can edit pieces of DNA. This alteration changes the instructions encoded in the DNA to correct the protein produced and restore proper cell function. There are various gene editing approaches currently under research, each with its own unique mechanisms. For instance, CRISPR Cas9 utilizes two main components, a guide RNA that locates the DNA sequence to be edited and a Cas enzyme or nuclease that cuts and edits the DNA at the specified location. Following this, the cell's natural DNA repair process takes place, resulting in a permanent desired change. Other gene editing techniques, such as TALENs and Zinc Finger Nucleases, may not necessarily involve the use of guide RNA or the scissor-like feature of the Cas9 enzyme.

2.4 CRISPR Gene Editing

CRISPR–CAS-associated protein (Cas) systems (CRISPR–Cas systems) originate from RNA-based bacterial defense systems [1]. They recognize and eliminate foreign DNA from invading plasmids and bacteriophage and are thus considered a type of bacterial immune system. The system detects and cuts bacteriophage genomes, saving fragments of them into repetitive CRISPR arrays as a record of previous infection so they can be targeted again in the future if they meet the same invader. This array is passed from generation to generation, growing with every new encounter. Diagram of a bacterial CRISPR locus indicating the genes included and CRISPR array. The CRISPR array of repeats and spacers is transcribed as a single pre-CRISPR transcript and the repeat regions bind the trans-activating CRISPR RNA (tracr RNA) in the locus. RNAse III then binds these double stranded sections and cleaves them, separating all the spacer and repeat pairs from the original single transcript,

producing lots of CRISPR RNA–tracer RNA fragments in which the spacer sequence is now known as a protospacer. These fragments bind Cas9, an RNA guided DNA endonuclease, activating and programing it to search the genome for protospacer adjacent motifs, which are often only three bases long. If it finds a PAM, Cas9 then unwinds the DNA and if there's a match between the protospacer in its CRISPR-RNA and the genomic DNA, Cas9 continues unwinding the DNA and cleaves the target. Most Cas9 systems used in labs create a blunt-ended DSB three bases away from the PAM sequence, offering predictable cleavage. While the CRISPR–Cas system is a natural process, in 2012, Professors Emmanuelle Charpentier and Jennifer Doudna were able to show that it was a programable system,18 for which they received the Nobel Prize in 2020. Since then, scientists have been able to adapt it, using short guide RNAs (sgRNAs) to make DSBs at the very specific locations they require, and take advantage of NHEJ or HDR to repair the break and introduce mutations or make desired alterations. Cas9 can be programed to make a DSB wherever the user wishes in the genome. To do this, the Cas9 endonuclease is only supplied with a sgRNA that combines a tracr and protospacer sequence and is typically 98–100 bases long, 20 bases of which is the protospacer. Rather than being a phage derived sequence, the protospacer sequence is chosen by the scientist to target their desired genome location for cleavage. Cleavage of a desired genomic sequence by supplying Cas9 with a sgRNA. The enzymes involved in strand cleavage are indicated. Unlike TALENs, this system can easily be multiplexed, cutting many targets at once. The different guide RNAs just need to be delivered into cells at the same time as Cas9. These can be delivered to cells in a number of ways, including transfection of plasmids encoding Cas9 and the sgRNAs, transfection of Cas9 messenger RNA (mRNA) and synthesized sgRNA, transfection of recombinant Cas9 protein and synthesized sgRNAs and lentivirus transduction to deliver Cas9 and sgRNA expression vectors. Each has its own pros and cons, and the choice of which to use will depend on factors such as cost, time, cell type and whether you wish to target a single point or are performing a whole genome screen. While CRISPR is very flexible, easy to use and good for multiplexing, it does make mistakes; this is useful in the setting of an adaptive immune system where bacteriophage may mutate to keep up with the arms race, but is not as helpful in genome modification. Cas9 will bind and sometimes cleave off-target sites that don't perfectly match the protospacer, generating unwanted mutations. Scientists, however, have come up with a number of approaches to limit this activity including Cas9 mutants with enhanced specificity.

Table 1 further therapeutic genetic approaches are RNA interference, ZFNs and TALENs, like described in detail.

Table 1. Overview of gene therapy strategies and FDA-/EMA-approved treatments

Gene Therapy Strategies	Mechanism
Gene Replacement	Transfer a functional copy of the gene to replace the nonfunctional copy, producing therapeutic levels of protein to reverse disease phenotype. Used in monogenic diseases due to single gene defect. *Luxturna (Voretigene Neparvovecrzyl) Strimvelis (GSK2696273) Zolgensma (Onasemnogene Abeparvovec-xioi) Zynteglo (Betibeglogene Autotemcel) Roctavian (Valoctocogene Roxaparvovec).
Gene Addition	Introduce an additional protein-coding gene to improve cellular function and homeostasis, improving disease phenotype. Used in complex disorders due to combined effects of multiple genes and environmental factors like cancer and heart diseases. Kymriah (Tisagenlecleucel) Yescarta (Axicabtagene ciloleucel) Tecartus (Brexucabtagene Autoleucel) Carvykti (Ciltacabtagene Autoleucel) Breyanzi (Lisocabtagene Maraleucel) Abecma (Idecabtagene Vicleucel).
Gene Silencing	Antisense Oligonucleotide; binds to target mRNA via complementary base pairing, altering pre-mRNA splicing, mRNA stability, transcription, or RNA-protein interaction to reduce deleterious protein levels. Spinraza (Nusinersen); Exondys 51 (Eteplirsen);Vyondys 53

Gene Therapy Strategies	Mechanism
	(Golodirsen); Milasen.
RNA Interference	Small interfering RNA represses gene expression by triggering RNA degradation and/or inhibiting protein synthesis. Onpattro (Patisiran); Givlaari (Givosiran); Oxlumo (Lumasiran).
Gene Editing	Programmable sequence-specific nucleases deliver genetic modification via double-strand break in specific genomic target sequence, followed by desired modifications during subsequent DNA break repair using HR or NHEJ. Widely used gene editing tools are ZFNs, TALENs, and CRISPR/Cas9 system.
ZFNs	First endonuclease fusing site-specific DNA-binding domain on zinc-finger protein to non-s sequence-specific DNA cleavage domain on Fok1 endonuclease. Fok1 endonuclease works as dimer for double-strand DNA cleavage at sites of binding of 2 ZFNs to opposite DNA strands.Clinical trials in various diseases.
TALENs	Assembled by fusing Fok1 cleavage domain to DNA-binding domain consisting of highly conserved repeat sequence from TALE that can associate with single or longer-sequence nucleotides. TALENs act as dimers for DNA cleavage. Clinical trials in various diseases.
CRISPR/Cas9 System	RNA-guided DNA cleavage module comprising single-stranded guide RNA and Cas9 endonuclease. Single-strand RNA binds to target sequence and Cas9 cleaves target DNA to generate double-strand break, with DNA repair through HR or NHEJ for targeted genomic modification. Clinical trials in various diseases.

3. DIFFERENT COMMON GENETIC PEDIATRIC DISEASES WITH THE OPTION OF GENE THERAPY

Leukemia, Lymphoma, and CAR T-cell Therapy: Leukemia and lymphoma are cancers caused by the overproduction of specific cells in the blood system, with the type of cancer depending on the type of cell overproduced. Blood stem cell transplants are used to treat these conditions, along with myeloma, myelodysplastic syndrome, and myeloproliferative disorders. During this treatment, the patient's faulty stem cells are removed through chemotherapy, followed by the replacement of healthy donor cells or modified patient cells in a procedure known as a bone marrow transplant or hematopoietic stem cell transplant. CAR T-cell therapy, a hybrid gene and cell therapy, is utilized for certain aggressive blood cancers by genetically reprogramming the patient's immune cells to target cancer cells.

Beta- Thalassemias and Hybrid Gene Cell Therapy: Beta-thalassemias are blood disorders resulting from abnormal hemoglobin production, leading to symptoms like anemia, fragile bones, and delayed growth. Treatment options include blood transfusions, medications, and cell therapy such as blood stem cell transplantation or hybrid gene cell therapy.

Melanoma in Childhood and Gene Therapy (Imlygic): Melanoma, a common skin cancer, is typically treated with surgery or BRAF inhibitors for advanced cases. Gene therapy like Imlygic can be used to target and destroy cancer cells in cases where surgery is not an option.

Cerebral Adrenoleukodystrophy and Hybrid Gene Cell Therapy (Skysona): Cerebral Adrenoleukodystrophy (CALD) is a genetic condition affecting the breakdown of fatty acids, leading to neurological symptoms. Treatment may involve medications, physiotherapy, or hybrid gene cell therapy like Skysona to break down accumulated fatty acids.

Metachromatic Leukodystrophy (MLD) and Hybrid Gene Cell Therapy (Libmeldy): MLD is a genetic disorder causing the accumulation of toxic fatty molecules in cells, leading to neurological symptoms. Treatment options include supportive care, blood stem cell transplants, or hybrid gene cell therapy like Libmeldy to break down accumulated molecules.

Spinal Muscular Atrophy (SMA) and Gene Therapy (Zolgensma): Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder that affects motor neurons, leading to muscle wasting. There are five subtypes of SMA, with symptoms ranging from general muscle

weakness to breathing difficulties. Traditional treatments focus on symptom management through therapy and surgery. In Europe, gene therapy (Zolgensma) is available for children under 24 months, aiming to restore nerve function by inserting a functional gene copy. While some clinics offer stem cell transplants for SMA, their effectiveness lacks scientific evidence.

Retinal Dystrophy and Gene Therapy (Luxturna): Retinal dystrophy encompasses genetic diseases damaging the retina, causing vision loss. Gene therapy, like Luxturna, targets specific retinal dystrophies such as retinitis pigmentosa and Leber congenital amaurosis, restoring vision if healthy cells remain in the retina and the mutation is in a specific gene (RPE65).

Gene Therapy for Hereditary Spastic Paraplegia Type 50: Personalized gene therapy offers hope for rare diseases like hereditary spastic paraplegia type 50 (SPG50). A gene replacement therapy trial successfully treated a 4-year-old patient, showing safety and potential efficacy in stabilizing the disease course. Further research is needed for long-term safety and efficacy confirmation.

Gene Therapy for Niemann Pick Disease Type C1 (NPC1): Niemann-Pick disease type C1 (NPC1) is a fatal neurodegenerative disorder with no approved treatments. Gene therapy studies in mouse models show promising results, suggesting early intervention before symptoms appear may offer the best outcomes for individuals with NPC1.

Gene Therapy for Giant Axonal Neuropathy: Giant axonal neuropathy, a rare neurodegenerative disorder, was treated with gene therapy in children, showing safety and potential benefits in motor function scores at specific doses. Further research is needed to assess the safety and effectiveness of this gene therapy.

4. DISCUSSION

Gene therapy in pediatrics is an innovative treatment approach for addressing various genetic disorders that present in childhood [2-6]. It entails altering or fixing a defective gene or inserting a healthy gene into the cells of a patient. There are over 7,000 paediatric genetic diseases (PGDs), with less than 5% having treatment options. Treatment approaches targeting different aspects of the disease's biological process have resulted in positive health outcomes for some patients with PGDs. Over the past 30 years, significant progress has been made in developing new therapies, including gene therapy, for numerous PGDs. Successful treatment outcomes depend on a thorough understanding of the genetic basis and disease mechanism. Gene therapy, in particular, has demonstrated effectiveness in various clinical trials, leading to regulatory approvals and opening the door for gene therapies for other PGDs. Different diseases present different challenges in the development of new therapies. Developing a gene therapy for a disease caused by a single gene mutation is less complex than developing a gene therapy for a disease caused by multiple genes or a combination of genetic and lifestyle factors. Some tissues and organs are also more accessible for cell extraction or therapy administration (e.g., blood or the eye). In gene and cell therapy, millions of cells need to be modified to achieve a successful effect, making the question of how to effectively administer the therapy an important aspect of development. Gene and cell therapies must undergo rigorous scientific, ethical, and regulatory scrutiny in the research and clinical trial phases, as well as potentially in the marketing phase. The journey from the lab to the bedside - from developing a treatment in the lab to its regular use in the clinic - takes many years. A study that shows promise in clinical trials may take several years to receive full approval from authorities, and there may be further delays between approval of a treatment and its availability through a national public health service. In recent years, gene therapy has made significant progress. More than 4000 protein-coding genes have been linked to over 6000 genetic diseases, and the use of next-generation sequencing has greatly improved the diagnosis of genetic disorders. While most genetic diseases are considered rare or very rare, with fewer than 1:100,000 cases, only one of the 12 approved gene therapies (excluding RNA therapies) targets an ultrarare disease. This article examines three gene supplementation therapy approaches that can be used for various rare genetic diseases: lentiviral vector-modified autologous CD34+ hematopoietic stem cell transplantation, systemic delivery of adeno-associated virus (AAV) vectors to the liver, and local AAV delivery to the cerebrospinal fluid and brain [7-9]. The success of gene therapy in treating genetic diseases depends on understanding the specific characteristics and function of the relevant gene, the genetic

changes that cause disease, and the regulatory systems that affect gene expression. This knowledge can be used to develop strategies tailored to different types of diseases. For monogenic recessive conditions where a nonfunctional gene leads to a protein defect, gene augmentation through gene replacement can be used to restore normal protein levels and reverse the disease phenotype. In more complex diseases involving multiple genes, gene addition may be necessary to improve cellular function and modulate the disease course. In dominant diseases, gene silencing strategies like ASO and RNA interference can be employed to suppress dysfunctional gene expression [10-16]. Advanced gene editing tools like ZFNs, TALENs, and CRISPR-Cas9 offer precise genetic modifications compared to traditional gene therapy methods. The choice of gene therapy approach depends on the therapeutic target and may involve in vivo or ex vivo delivery methods using viral vectors or non-viral systems. Regulating transgene expression is crucial to avoid toxicity, and strategies to enhance therapeutic efficacy include increasing target-cell specificity, reducing immunogenicity, and delivering the transgene to immune privileged sites. Despite challenges and setbacks in the field, ongoing research aims to improve gene therapy technologies with minimal risks. The approval of Glybera in 2012 marked a milestone in gene therapy, leading to trials for various monogenic diseases [18-21]. While Glybera was later withdrawn due to cost and rarity of the disease it treated, research and development of novel gene therapies for genetic diseases continue to progress. There are currently 11 gene therapy products available commercially. These include Luxturna, Zolgensma, Roctavian, CAR-T therapies (Yescarta, Kymriah, Tecartus, Carvykti, Breyanzi, and Abecma), Zynteglo, and Strimvelis. Kymriah and Luxturna are approved for use in Singapore under the CTGTP regulatory framework. Therapeutic advances have been made in ADA-SCID, TDT, and SMA with gene-selective therapies [22-25].

5. CONCLUSION

Gene and cell therapies undergo rigorous scientific, ethical, and regulatory scrutiny during the phases of research and clinical testing and potentially during the marketing phase. The journey from the laboratory to the patient's bedside - from the development of a treatment in the lab to its regular use in the clinic takes many years. Studies have shown promise in clinical trials may take several years to be fully approved by regulatory authorities, and there may be further delays between the approval of a treatment and its availability through a national public health service. The development of genomic technologies has brought about a significant change in how patients with PGDs are treated, moving from diagnosis to treatment. The high expense of gene-specific therapies and the challenges in securing coverage and reimbursement pose a significant barrier to patients seeking these treatments. In order to make precision medicine a reality for improved patient-focused care in the coming years, collaboration among all involved parties is essential to create new reimbursement strategies that ensure all patients can benefit from these therapies.

Rare pediatric neurogenetic diseases typically manifest early in life, lack specific treatment options, have high mortality rates, and present a significant threat to children's health and survival. Adeno-associated virus (AAV)-mediated gene therapy, a form of disease-modifying treatment, offers a novel approach to addressing these conditions and represents a major breakthrough in the field. Currently, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved AAV-mediated gene therapy products for spinal muscular atrophy, aromatic L-amino acid decarboxylase deficiency, and Duchenne muscular dystrophy. Recent preclinical and clinical trial data suggest that AAV-mediated gene therapy holds great promise for the treatment of genetic disorders. The expedited approval process for rare disease treatments may offer hope for children with rare neurogenetic conditions. However, AAV-mediated gene therapy comes with inherent risks and challenges, underscoring the need for standardized regulatory oversight and robust long-term monitoring to assess its effectiveness and safety. Additive gene therapies in research are focus of interest, which are clearly divided in Table 1. A one-time genetic approach is desirable in many rare pediatric diseases and established only in few pediatric diseases to date. Research in this field is running fast by biopharmaceutical companies to develop prize-intensive therapies for all these rare or ultrarare pediatric populations.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AI technologies such as Large Language Models

(ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/122475