Gene Therapy as a Treatment Modality for Severe Combined Immunodeficiency: A Narrative Review

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Abstract

Introduction: Severe combined immunodeficiency (SCID) is a life-threatening genetic disorder marked by severe T-cell defects and often B-cell and NK-cell dysfunction, leading to an increased risk of infections. Treated via gene therapy which is the introduction of modified therapeutic genes either ex vivo or in vivo as a DNA segments.

Methods: A Narrative review was conducted followed. Literature was searched on Midline, PubMed central (PMC), Web of science, Elsevier, Scopus using the following keywords: Severe combined immunodeficiency (SCID), gene therapy and genetic disorders between 2015 and 2024. The included papers were case reports and series, cohort studies, case control and randomized controlled trials.

Results: The reviewed literature illustrate that gene therapy has reached significant progress in treating (SCID), particularly X-linked SCID (SCID-X1) and ADA-SCID. Viral vectors especially retroviral, lentiviral, and adeno-associated viral (AAV) vectors have been successfully used to recover T-cell immunity and correct genetic defects, with ADA-SCID patients showing stable immune function and reduced adoption on enzyme replacement therapy. The Protection of lentivirus and foamy virus vectors have been improved, reducing dangers like insertional mutagenesis. Despite their biosafety enhancement, non-viral delivery methods are still limited by their lower transfection efficiency.

Conclusion: gene therapy can treat numerous different primary immunodeficiency (PIDs). There are some limits. Important elements to consider are vector and envelope type, transduction technique, cell dose, delivery modality, conditioning regimen, and illness features. Further research is needed.

INTRODUCTION

Gene therapy encompasses the introduction of new therapeutic genes, as DNA segments, modification of existing genes, or the introduction of RNA into cells, with the aim of preventing, treating, or curing disorders and diseases in order to restore or add gene expression. Diseases such as diabetes, Parkinson's disease, heart failure, cancers, and neurodegenerative and metabolic disorders have been well managed through gene therapy.[1] Gene therapy is increasingly being recognized as an efficient therapeutic modality to treat primary immunodeficiency diseases.[19] In the context

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of these therapies, cells can undergo modification either ex vivo before subsequent administration to humans or in vivo through direct gene therapy administration, (Figure 1).[2]

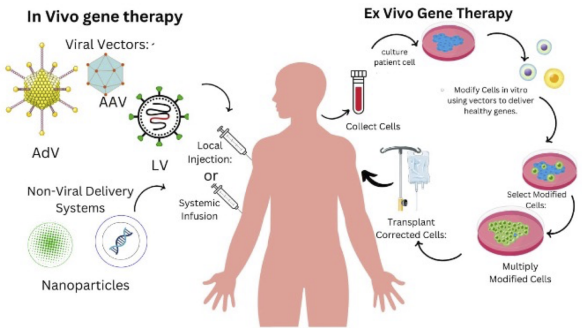

Figure 1: Gene therapy modalities; in vivo gene therapy and ex vivo gene therapy.

The initial step in vivo gene therapy is to introduce a therapeutic gene into an appropriate vector, which can be either viral or non-viral. Adeno-associated viral (AAV) vectors are most frequently used. Following that, the patient receives a systemic infusion or local injection of the vector containing the therapeutic gene. The vector is used to transport the therapeutic gene to the patient's body's target cells.[3] Ex vivo gene therapy begins with the patient's body utilized to extract the cells that will be altered, such as T-cells or stem cells. The therapeutic gene is then transferred to the patient's cells outside the body via an appropriate vector, and the modified cells are reintroduced into the patients. Cellular and gene therapies have evolved to encompass a wide range of conditions, including single-gene disorders, polygenic disorders, various forms of cancer, vascular diseases, neurodegenerative disorders, inflammatory conditions and acquired diseases. Numerous ongoing clinical studies continue to expand the spectrum of target diseases. Gene therapy offers new options for the treatment of inherited immunological diseases such as SCID.[16] As essential tools of gene therapy, vectors transfer genetic material (DNA or RNA) to target cells, with instructions to modulate the cellular production of a protein or a group of proteins. Vectors for gene delivery are traditionally categorized as viral and non-viral vectors. Gene therapy trials have featured a wide spectrum of vectors and delivery techniques as illustrated by (Supplementary Table 1), with viral vectors being employed in approximately two-thirds of trials as of 2023 as the predominant choice.[4]

METHODS

This research employed a narrative review design to summarize and synthesize current evidence on the Structured Clinical Interview for (SCID) from studies indexed in major scientific databases WEB OF SCIENCE, SCOPUS, MEDLINE, focusing on publications from January 2020 to December 2025 (Supplementary Table 2). Narrative review methodology was chosen to provide a descriptive and integrative overview of developments in evaluation, applications, and adaptations of SCID across research settings.

Discussion

An ideal gene therapy vector delivers a therapeutic gene while ensuring long-term expression in target cells with excellent reliability and efficiency. Gene delivery is accomplished using a variety of viral vectors differentiated by RNA or DNA genomes, including adenovirus, Adeno associated viruses (AAV), lentivirus (LVs), murine retrovirus, and HSV.[5] Viral vectors are still the most efficient vehicles for gene transfer in gene therapy.[17] LVs produced from HIV can deliver therapeutic genes into the host genome for persistent expression, and they are safe and able to infect both dividing and non-dividing cells. LVs are therefore perfect for the treatment of long-term illnesses like diabetes and Parkinson's disease. Lentiviral vectors are considered safer than the previous retroviral systems, reducing the risk of insertional mutagenesis.[22] Adenoviral vectors (AdVs), which have a significant transduction efficacy, are

beneficial for a variety of cell types. Despite their restricted tissue range, AAV vectors are the primary conduit of authorized gene treatments, and new research has improved their transduction mechanisms. Among the most promising delivery systems are adeno-associated viral vectors, because of their improved transduction efficiency and safety profile.[18] All things considered, the advancement of gene therapy relies on LVs, AdVs, and AAVs.[4] Although viral vectors are more efficient in transfecting host cells than nonviral techniques, their immunogenicity and cytotoxicity make them undesirable. Nonviral vectors have significant safety advantages over viral techniques, including reduced pathogenicity, lower cost, and ease of manufacture. Biosafety is the primary benefit of utilizing nonviral vectors in gene therapy. On the other hand, nonviral gene transfer has long been disregarded because of its low transport efficiency, which leads to minimal transgenic expression in the short term. Although microinjection, which uses a needle to introduce genetic material with no vector, is simple, it is inefficient because of phagocyte and nuclease clearance. It cures cancer, liver, skin, and muscles. Ballistic DNA uses high-velocity metal particles for ovarian cancer research, but it demands exact speed. Electroporation uses an electric field to produce membrane pores, which improves gene delivery for intratumoral administration and DNA vaccination, with efficiency varying depending on the pulse parameters. Magnetofection is a technique for delivering specific genes using magnetic nanoparticles and an external magnetic field. Hydroporation uses hydrodynamic pressure to transfer genes. Liposomes transport both water and lipid-soluble medicines, producing lipoplexes for cellular uptake.[6] SCIDs are inherited disorders characterized by a significant halt in T cell development, which may be coupled with abnormalities in other lymphoid (or, in rare cases, myeloid) lineages. The most common of the 16 genetic SCID illnesses reported so far are X-linked SCID (SCID X1) and ADA deficiency. Patients with untreated SCID have a variety of infectious problems and perish within their first year of life. SCIDs can be successfully treated with allogeneic HSCT, which corrects T cell deficit for the long term. [7] Gene therapy of hematopoietic stem cells provides an important therapeutic strategy for several primary immunodeficiencies.[13] However, HSCT with non-genoidentical donor transplants was associated with relatively high mortality and morbidity rates, possibly due to a graft-versus-host reaction or, if the donor's marrow graft was low of T cells, delayed T cell reconstitution. [8] As part of gene therapy, viral vectors are used to deliver a functional copy of the IL2RG gene, which is mutated in individuals with X-linked Severe Combined Immunodeficiency (X-SCID). The most popular strategy is the use of retroviral vectors, which have been demonstrated to successfully restore T-cell immunity (Figure 2).

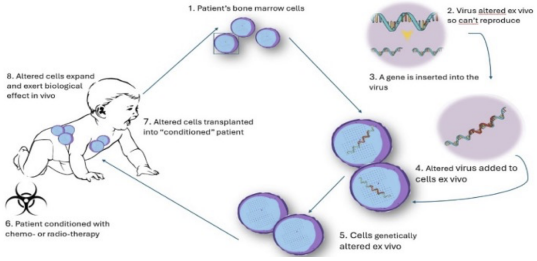

Figure 2: A schematic representation of gene therapy protocol used in SCID-X1 patients

Therapies based on lentiviral vectors have proved effective in restoring immune function in infants diagnosed with SCID-X1.[12] However, insertional mutagenesis can also lead to leukemia. Lentivral vectors are thought to be safer and more effective because to their successful clinical trial results and less danger of insertional mutagenesis. Foamy virus vectors offer a more contemporary option that integrates less frequently around oncogenes and may lower the danger of leukemia.[9] Novel alpharetroviral vector systems may offer safer alternatives for future SCID gene therapy approaches.[20] Gammaretroviral vectors are used in gene therapy for ADA-SCID to transduce the ADA

gene into cells obtained from bone marrow. Retroviral gene therapy has shown long-term therapeutic benefit in patients with ADA deficiency.[21] Long-term therapeutic benefits have been shown by this method, as patients have shown improved immune function and stable multilineage gene marking. Recent clinical studies have shown that lentiviral gene therapy provides durable immune reconstitution in ADA-SCID patients and reduces the need for enzyme replacement therapy.[11] The treatment uses low-dose chemotherapy in conjunction with cytoreductive conditioning to promote gene-modified cell engraftment. This method has provided conclusive treatment for ADA-SCID, reducing the need for enzyme replacement medication while significantly restoring immunity, (Supplementary Table 3).[10] Significant progress has been made in gene therapy for ADA-SCID, leading to improved survival and immune recovery.[14]

Conclusion

Gene therapy for two SCIDs has been developed over 20 years and is now safe and effective. Technological advancements have led to new tools that may expand the indication. Recent advancements in lentiviral vectors have significantly improved safety profiles, reducing the risk of insertional mutagenesis. Recent advances in gene-editing techniques such as CRISPR could enable the precise correction of genetic mutations responsible for SCID.[15] CRISPR-based gene editing offers precise correction of genetic defects and is under active investigation. Newborn screening programs are enabling earlier diagnosis and treatment, improving outcomes. However, challenges remain in ensuring global accessibility, affordability, and long-term monitoring of gene therapy recipients. Future research should focus on refining delivery methods, minimizing risks, and expanding access to these lifesaving therapies. As previously noted, gene therapy has the potential to treat numerous different PIDs. There are some limits. Important elements to consider are vector and envelope type, transduction technique, cell dose, delivery modality, conditioning regimen, and illness features. Further research is needed.

Conflict of Interest

The authors declare that they have no competing interests.

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