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RESEARCH ARTICLE

GENE THERAPY AND ENZYME REPLACEMENT THERAPY: THERAPEUTIC PARADIGMS FOR GENETIC DISORDERS

Dr. Deepali Vaishnav[1], Dr. Manjusha Hivre[2],* and Dr. Shrirang Holkar[2]

[1]Professor and HOD, Department of Biochemistry, MGM Medical College, Chhatrapati Sambhajinagar; [2]Associate Professor, Department of Biochemistry, MGM Medical College, Chhatrapati Sambhajinagar

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***Corresponding author:**
Dr. Manjusha Hivre

ABSTRACT

Gene therapy and enzyme replacement therapy (ERT) represent two pivotal therapeutic approaches for treating genetic disorders characterized by enzyme deficiencies. While ERT provides symptomatic relief through direct enzyme supplementation, gene therapy aims to address the underlying genetic cause by introducing functional genes into target cells. This review examines the mechanisms, clinical applications, advantages, limitations, and future prospects of both therapeutic modalities, with particular emphasis on their comparative efficacy in treating lysosomal storage disorders, primary immunodeficiencies, and other genetic conditions. As of 2024, 3,900 gene therapy clinical trials have been completed, are ongoing or have been approved worldwide, while 36 gene therapies are approved by the FDA, with an additional 500 in the pipeline and the expectation that 10–20 will be approved annually by 2025.

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INTRODUCTION

Genetic disorders affecting enzyme function represent a significant clinical challenge, affecting millions of individuals worldwide. These conditions, often resulting from single gene defects, lead to enzyme deficiencies that disrupt normal cellular metabolism and cause progressive organ dysfunction. Two primary therapeutic strategies have emerged to address these disorders: enzyme replacement therapy (ERT), which provides exogenous enzyme supplementation, and gene therapy, which seeks to restore endogenous enzyme production through genetic modification. The development of these therapeutic approaches has revolutionized the treatment landscape for previously untreatable genetic conditions. ERT, first successfully implemented in the 1990s for Gaucher disease, demonstrated that direct enzyme supplementation could ameliorate disease symptoms and improve patient outcomes (1,2). Subsequently, advances in molecular biology and vector technology have made gene therapy a viable alternative, offering the potential for long-term correction of genetic defects (3,4).

MATERIALS AND METHODS

Literature Search Strategy: A comprehensive systematic literature review was conducted to identify relevant studies on gene therapy and enzyme replacement therapy for genetic disorders. The search was performed using multiple electronic databases including PubMed/MEDLINE, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov from inception through Jan 2025. Search Terms and Strategy: The following search terms were used individually and in combination using Boolean operators (AND, OR):"Gene therapy" OR "genetic therapy" OR "gene transfer","Enzyme replacement therapy" OR "ERT" OR "enzyme supplementation", "Lysosomal storage disease" OR "lysosomal storage disorder" OR "LSD", "Adeno-associated virus" OR "AAV" OR "lentiviral vector" OR "retroviral vector", "Primary immunodeficiency" OR "SCID" OR "adenosine deaminase deficiency", "Hemophilia" OR "factor VIII" OR "factor IX", "Gaucher disease" OR "Fabry disease" OR "Pompe disease" OR "mucopolysaccharidosis""Clinical trial" OR "randomized controlled trial" OR "phase I" OR "phase II" OR "phase III", "Safety" OR "efficacy" OR "adverse events" OR "immunogenicity", "Cost-effectiveness" OR "economic evaluation" OR "pharmacoeconomics"

Database-Specific Search Strategies: *PubMed/MEDLINE:* ((("Gene Therapy"(Mesh) OR "Genetic Therapy"(Mesh)) OR ("gene therapy"(tiab) OR "genetic therapy"(tiab) OR "gene transfer"(tiab))) OR (("Enzyme Replacement Therapy"(Mesh)) OR ("enzyme replacement therapy"(tiab) OR "ERT"(tiab) OR "enzyme supplementation"(tiab)))) AND (("Lysosomal Storage Diseases"(Mesh) OR "Primary Immunodeficiency

Diseases"(Mesh) OR "Hemophilia A"(Mesh) OR "Hemophilia B"(Mesh)) OR ("lysosomal storage"(tiab) OR "primary immunodeficiency"(tiab) OR "hemophilia"(tiab) OR "genetic disorder"(tiab)))

EMBASE: ('gene therapy'/exp OR 'genetic therapy'/exp OR 'gene therapy':ab,ti OR 'genetic therapy':ab,ti) OR ('enzyme replacement therapy'/exp OR 'enzyme replacement therapy': ab,ti OR 'ert':ab,ti) AND ('lysosomal storage disease'/exp OR 'primary immunodeficiency'/exp OR 'hemophilia'/exp OR 'genetic disease'/exp)

Inclusion and Exclusion Criteria

Inclusion Criteria

- Original research articles, clinical trials, systematic reviews, and meta-analyses
- Studies published in English language
- Human studies (clinical trials, case series, observational studies)
- Preclinical studies with direct clinical relevance
- Studies focusing on gene therapy or enzyme replacement therapy for genetic disorders
- Regulatory documents and clinical practice guidelines
- Economic evaluations and cost-effectiveness studies
- Studies published from 1990 to Jan 2025

Exclusion Criteria

- Case reports with fewer than 5 patients
- Studies not published in English
- Conference abstracts without full-text availability
- Studies focusing solely on diagnostic methods
- Veterinary studies without human relevance
- Studies on gene therapy for acquired diseases (cancer, cardiovascular disease) unless directly relevant to genetic disorders
- Duplicate publications and redundant data

Study Selection Process

The study selection process followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines:

- **Initial Screening:** Titles and abstracts of all identified records were independently screened by two reviewers (DMV. and SRH.) using predefined inclusion/exclusion criteria.
- **Full-Text Review:** Full-text articles of potentially eligible studies were retrieved and independently assessed by the same two reviewers.
- **Consensus Meeting:** Disagreements between reviewers were resolved through discussion, and when necessary, consultation with a third reviewer (MDH.).
- **Reference Screening:** Reference lists of included studies and relevant review articles were manually searched to identify additional studies.
- **Clinical Trial Registry Search:** ClinicalTrials.gov, European Clinical Trials Database (EudraCT), and WHO International Clinical Trials Registry Platform were searched for ongoing and completed trials.

Data Extraction: Data extraction was performed using the following information systematically extracted from each included study:

Study Characteristics: Author, year of publication, journal, Study design (RCT, cohort, case series, etc.)**,** Study location and setting**,** Sample size and population characteristics**,** Follow-up duration

Population Characteristics: Age at treatment initiation**,** Disease type and severity**,** Previous treatments**,** Baseline clinical parameters**,** Genetic mutations (when reported).

Intervention Details: Type of therapy (gene therapy vs. ERT)**,** Specific agent/vector used**,** Dosing regimen and administration route**,** Treatment duration**,** Concomitant medications.

Outcome Measures: Primary and secondary endpoints**,** Efficacy outcomes (clinical, biochemical, functional)**,** Safety outcomes (adverse events, immunogenicity)**,** Quality of life measures**,** Economic outcomes**,** Long-term follow-up data.

Gene Therapy Specific Data: Vector type and serotype**,** Gene construct details**,** Delivery method**,** Expression levels achieved**,** Vector-related adverse events**,** Anti-vector antibodies.

ERT Specific Data: Enzyme type and source**,** Infusion schedule and duration**,** Dose modifications**,** Infusion-associated reactions**,** Anti-drug antibodies**,** Treatment interruptions

Quality Assessment, Data Synthesis and Analysis: The methodological quality of included studies was assessed using appropriate tools based on study design. Given the heterogeneity of study designs, populations, and outcomes, a narrative synthesis approach was employed. Data synthesis included: Quantitative Analysis, Qualitative Analysis, Subgroup Analyses.

Regulatory and Economic Data Collection

Regulatory Information: FDA approval dates and indications, EMA approval status, Orphan drug designations, Clinical trial phases and status, Post-market surveillance data.

Economic Data: Treatment costs (acquisition, administration, monitoring), Cost-effectiveness analyses, Budget impact assessments, Health technology assessments, Reimbursement decisions.

Genetic disorders affecting enzyme function represent a significant clinical challenge, affecting millions of individuals worldwide. These conditions, often resulting from single gene defects, lead to enzyme deficiencies that disrupt normal cellular metabolism and cause progressive organ dysfunction. Two primary therapeutic strategies have emerged to address these disorders: enzyme replacement therapy (ERT), which provides exogenous enzyme supplementation, and gene therapy, which seeks to restore endogenous enzyme production through genetic modification. The development of these therapeutic approaches has revolutionized the treatment landscape for previously untreatable genetic conditions. ERT, first successfully implemented in the 1990s for Gaucher disease, demonstrated that direct enzyme supplementation could ameliorate disease symptoms and improve patient outcomes (1,2). Subsequently, advances in molecular biology

and vector technology have made gene therapy a viable alternative, offering the potential for long-term correction of genetic defects (3,4).

Enzyme Replacement Therapy

Mechanism of Action: Enzyme replacement therapy involves the intravenous administration of recombinant enzymes designed to substitute for deficient or dysfunctional endogenous enzymes. The therapeutic enzymes are typically produced using recombinant DNA technology in mammalian, bacterial, or plant cell culture systems (5,6). These enzymes must retain their catalytic activity, demonstrate appropriate tissue distribution, and maintain stability in the physiological environment. The success of ERT depends on several critical factors including enzyme uptake by target cells, intracellular trafficking to appropriate subcellular compartments, and maintenance of enzymatic activity (7). For lysosomal enzymes, uptake occurs primarily through mannose-6-phosphate receptor-mediated endocytosis, allowing the recombinant enzymes to reach their intended lysosomal destination (8,9).

Clinical Applications: ERT is currently approved for eight LSDs in the United States, with extensive clinical validation demonstrating efficacy across multiple genetic disorders:

Gaucher Disease: Alglucerase and imiglucerase for Type 1 Gaucher disease represent the first successful applications of ERT. These therapies target glucocerebrosidase deficiency and have demonstrated significant improvements in hepatosplenomegaly, hematological parameters, and bone disease (10,11).

Fabry Disease: Agalsidase alfa and agalsidase beta address α-galactosidase A deficiency, reducing globotriaosylceramide accumulation and improving cardiac, renal, and neurological manifestations (12,13).

Pompe Disease: Alglucosidase alfa targets acid α-glucosidase deficiency, showing particular efficacy in infantile-onset disease and providing benefits in late-onset presentations (14,15). Although enzyme replacement therapy has substantially improved outcomes for patients with lysosomal storage disorders, limitations of this therapy have become apparent throughout two decades of use.

Mucopolysaccharidoses: Multiple ERTs have been developed for various MPS subtypes, including laronidase for MPS I, idursulfase for MPS II, and galsulfase for MPS VI, among others (16,17).

Primary Immunodeficiencies: Adenosine deaminase deficiency can be treated with pegademase bovine, addressing the metabolic consequences of ADA deficiency (18,19).

Advantages of ERT: ERT offers several significant advantages as a therapeutic approach. The treatment provides immediate biochemical correction, rapidly reducing substrate accumulation and improving cellular function (20). The therapeutic effect is predictable and dose-dependent, allowing for optimization of treatment regimens based on individual patient responses. The efficacy and safety of ERT for LSDs has been confirmed by extensive clinical trials. The reversible nature of ERT allows for treatment discontinuation if necessary, and the therapy can be combined with other therapeutic modalities (21). Additionally, ERT does not involve genetic modification, avoiding concerns related to insertional mutagenesis or immune responses to viral vectors (22).

Limitations of ERT: Despite its successes, ERT faces several significant limitations. The cost of ERT is very high, creating problems for third-party payers, which has strained reimbursement schemes based on the demonstration of acceptable cost effectiveness. The requirement for lifelong, frequent intravenous infusions (typically every two weeks) creates substantial treatment burden and impacts quality of life (23). ERT may help slow progression and improve clinical symptoms, but it cannot affect neurologic features due to its inability to cross the blood-brain barrier. However, there are still obstacles to successful ERT, such as immune reactions against the infused enzyme, mistargeting of enzymes rather than lysosomes, and intractable tissues. Immune responses to the therapeutic enzymes can develop, potentially reducing treatment efficacy through neutralizing antibodies or infusion-associated reactions (24,25). The therapy provides only temporary biochemical correction, requiring continuous treatment to maintain therapeutic benefits (26).

Gene Therapy

Mechanism of Action: Gene therapy aims to introduce functional genes into target cells to restore normal enzyme production and correct the underlying genetic defect. This approach can be implemented through various strategies including gene addition (introducing a functional copy of the defective gene), gene editing (correcting specific mutations), or gene silencing (reducing expression of dominant negative proteins) (27,28). The success of gene therapy depends on efficient gene delivery, appropriate gene expression levels, and long-term persistence of therapeutic benefit. Vector systems must demonstrate tissue tropism for relevant target organs, avoid eliciting harmful immune responses, and maintain stable gene expression over time (29,30).

Vector Systems

Viral Vectors: Multiple viral vector systems have been developed for gene therapy applications, each with distinct advantages and limitations. Adeno-associated virus (AAV) vectors have emerged as the leading platform for gene therapy, offering excellent safety profiles, broad tissue tropism, and long-term gene expression in non-dividing cells (31,32). Different AAV serotypes demonstrate varying tissue preferences, enabling targeted delivery to specific organs such as liver, muscle, or central nervous system (33,34).

Lentiviral vectors, derived from HIV, can integrate into the host genome and provide sustained gene expression in dividing cells. These vectors have shown particular promise for hematopoietic stem cell gene therapy applications (35,36). Retroviral vectors were among the first successful gene therapy vectors but have been largely superseded by safer alternatives due to insertional mutagenesis risks (37,38).

Non-viral Vectors: Physical methods such as electroporation, lipofection, and direct injection offer alternative delivery approaches, though generally with lower efficiency than viral vectors (39,40).

Clinical Applications: Gene therapy has achieved remarkable clinical success across multiple genetic disorders:

Severe Combined Immunodeficiency (SCID): Gene therapy for ADA-SCID and X-linked SCID using retroviral and lentiviral vectors has demonstrated curative potential, with

many patients achieving immune reconstitution and long-term survival (41,42).

Hemophilia: AAV-mediated gene therapy for hemophilia A and B has shown sustained increases in factor levels, reducing bleeding episodes and factor concentrate requirements (43,44).

Leber Congenital Amaurosis: Luxturna, an AAV-based gene therapy for RPE65-associated LCA, was the first FDA-approved gene therapy for an inherited disease, demonstrating improved vision in treated patients (45,46).

Spinal Muscular Atrophy: Zolgensma, an AAV-based gene therapy delivering the SMN1 gene, has shown remarkable efficacy in treating SMA, particularly when administered early in disease progression (47,48).

Beta-thalassemia and Sickle Cell Disease: Lentiviral gene therapy approaches have achieved transfusion independence in multiple patients with severe hemoglobinopathies (49,50).

Advantages of Gene Therapy: Gene therapy offers the potential for curative treatment by addressing the root cause of genetic disorders rather than merely treating symptoms (51). Successful gene therapy can provide long-lasting therapeutic benefits, potentially eliminating the need for chronic treatment (52). The approach can effectively treat central nervous system manifestations by achieving local gene expression within the brain and spinal cord (53,54).

Gene therapy may be more cost-effective in the long term, despite high upfront costs, by eliminating the need for lifelong enzyme replacement (55). The treatment can achieve physiological regulation of enzyme expression and has the potential to treat disorders where ERT is ineffective or unavailable (56).

Limitations of Gene Therapy: Gene therapy faces several significant challenges and limitations. Immune responses to viral vectors or transgene products can limit efficacy and pose safety risks (57,58). The potential for insertional mutagenesis, while reduced with newer vector systems, remains a theoretical concern (59,60). Manufacturing complexity and cost create barriers to widespread implementation (61).

Limited redosing capability due to anti-vector immunity restricts treatment options if initial therapy proves inadequate (62). Achieving appropriate gene expression levels across different tissues remains challenging, and long-term safety data are still being accumulated for many gene therapy products (63,64).

Comparative Analysis

Efficacy Comparison: The relative efficacy of gene therapy versus ERT varies significantly depending on the specific disorder, affected tissues, and individual patient factors. For systemic manifestations readily accessible to circulating enzymes, ERT often provides effective treatment with predictable dose-response relationships (65). However, gene therapy may achieve superior outcomes for central nervous system involvement and in tissues with poor enzyme uptake (66,67). Gene therapy's potential for providing sustained therapeutic benefit contrasts with ERT's requirement for continuous treatment. In conditions such as hemophilia and SCID, gene therapy has demonstrated curative potential, while ERT provides symptomatic management without addressing the underlying genetic defect (68,69).

Safety Profiles: ERT generally demonstrates favorable short-term safety profiles, with infusion-associated reactions and immune responses representing the primary concerns (70). The reversible nature of ERT allows for immediate treatment discontinuation if adverse events occur (71). Gene therapy safety considerations include acute immune responses to vectors, potential long-term effects of genetic modification, and manufacturing-related impurities (72,73). While serious adverse events have been rare in recent clinical trials, the long-term safety profile continues to be evaluated (74).

Cost Considerations: Both therapies involve substantial costs, though through different mechanisms. ERT requires ongoing manufacturing, distribution, and administration costs throughout the patient's lifetime (75). Gene therapy involves high upfront development and manufacturing costs but may prove more cost-effective over extended time periods by eliminating the need for chronic treatment (76,77). Economic analyses suggest that gene therapy may be cost-effective for severe, early-onset disorders where lifelong ERT would be required (78). However, the high initial costs of gene therapy create challenges for healthcare system adoption and patient access (79).

Patient Considerations: Patient preferences, lifestyle factors, and individual circumstances significantly influence treatment choice. ERT's reversible nature and established safety profile may appeal to some patients, while others may prefer gene therapy's potential for long-term correction despite higher uncertainty regarding long-term outcomes (80). The treatment burden associated with regular ERT infusions contrasts with gene therapy's single or limited administration schedule (81). However, gene therapy requires specialized treatment centers and may involve more intensive monitoring protocols (82).

Combination Approaches and Emerging Strategies: Emerging therapeutic strategies explore combining gene therapy and ERT to optimize treatment outcomes. Sequential approaches might involve initial ERT to stabilize patients followed by gene therapy for long-term correction (83). Concurrent administration could potentially enhance gene therapy efficacy while providing immediate therapeutic benefit (84). Genetic substrate reduction therapy (gSRT), which involves the use of nucleic acids to downregulate the genes involved in the biosynthesis of storage substances, has been investigated in the treatment of lysosomal storage diseases. This approach represents an additional therapeutic modality that can be combined with both ERT and gene therapy (85). Combination approaches may be particularly valuable for severe, rapidly progressive disorders where immediate intervention is critical, but long-term genetic correction is desired (86). Research continues to evaluate optimal timing, dosing, and patient selection for combined therapeutic strategies (87).

Future Directions

Technological Advances: CRISPR Therapeutics initiated two phase 1 trials for additional targets for cardiovascular disease, highlighting the expanding applications of gene editing technologies. CRISPR-based gene editing technologies offer

precise correction of genetic defects without requiring ongoing gene expression from viral vectors (88,89). Base editing and prime editing techniques enable correction of point mutations without double-strand breaks (90,91). Advances in manufacturing processes are reducing gene therapy costs and improving scalability (92). Novel AAV capsids with enhanced tissue tropism and reduced immunogenicity are being developed (93,94).

ERT Innovations: Next-generation enzyme replacement therapies incorporate various strategies to improve efficacy and reduce treatment burden. Novel nanotechnology-driven enzyme replacement strategies for lysosomal storage disorders are being developed to address current limitations. Substrate reduction therapy combined with ERT may enhance therapeutic outcomes (95). Extended half-life enzymes through PEGylation or other modifications could reduce infusion frequency (96,97). Targeted delivery systems using cell-penetrating peptides or receptor-mediated approaches may improve tissue penetration (98). Oral enzyme replacement formulations are being investigated to improve patient convenience and compliance (99).

Personalized Medicine: Advances in genetic testing and biomarker identification enable more precise patient selection and treatment optimization (100). Pharmacogenomic approaches may predict individual responses to gene therapy or ERT (101). Personalized vector design based on patient-specific factors could improve gene therapy outcomes (102).
In September 2024, Denali Therapeutics plans to seek accelerated FDA approval for DNL310 in Hunter Syndrome, showing substantial improvements in biomarkers and clinical outcomes, demonstrating the ongoing advancement in personalized therapeutic approaches.

Regulatory Considerations: Both ERT and gene therapy face complex regulatory landscapes that continue to evolve. ERT follows established pathways for biological products, with extensive experience in clinical development and post-market surveillance (103). Gene therapy regulatory frameworks are newer and continue to develop as the field advances (104).
Regulatory agencies are working to streamline approval processes while maintaining appropriate safety standards (105). Adaptive trial designs and accelerated approval pathways may facilitate faster access to life-saving therapies (106). International harmonization efforts aim to reduce regulatory complexity for global development programs (107).

CONCLUSION

Gene therapy and enzyme replacement therapy represent complementary approaches to treating genetic disorders, each offering distinct advantages and limitations. ERT of LSDs represents the most important advance in the treatment of this class of diseases, providing immediate, predictable therapeutic benefit with established safety profiles but requiring lifelong treatment and facing challenges in addressing all disease manifestations. Gene therapy offers the potential for curative treatment by correcting underlying genetic defects but involves greater complexity and uncertainty regarding long-term outcomes. The choice between these therapeutic approaches must consider multiple factors including disease severity, affected organ systems, patient preferences, and available resources.

As both fields continue to advance, the therapeutic landscape will likely include increasingly sophisticated applications of each approach, as well as innovative combination strategies. Future developments in vector engineering, enzyme design, manufacturing processes, and personalized medicine approaches will continue to improve outcomes for patients with genetic disorders. The success achieved with both ERT and gene therapy demonstrates the potential for translating scientific advances into meaningful clinical benefits. Continued research, clinical development, and regulatory evolution will further expand therapeutic options and improve outcomes for patients with genetic disorders worldwide.

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