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GENE THERAPY AS A SOLUTION FOR GENETIC DISORDERS IN PEDIATRIC POPULATIONS

Niaz Ullah[1], Muhammad Konain Azhar[2], Syed Mazhar Ali Shah[3], Maqsood Razzaq[4], Muhammad Amir Parvaiz[5], Muhammad Abdullah Awan[*6], Mashal Afzal[7]

[1]*MPhil Genetics, Islamia College University, Peshawar, Pakistan*
[2]*MBBS Student, Shenyang Medical College, China.*
[3]*Resident Paediatrician MTI Mardan Medical Complex, Mardan, Pakistan.*
[4]*Department of Genetics, University of Central Punjab, Lahore, Pakistan*
[5]*BS AHS Pathology Lab Science, University of Sargodha, Pakistan*
[*6]*MBBS final year, Wah Medical College, Pakistan*
[7]*MBBS, Bolan Medical College, Quetta, Pakistan*

[2]ORCID: 0009-0002-2196-6341, [3]ORCID:0009-0007-3269-4288,
[5]ORCID: 0009-0001-5100-6512, [*6]ORCID: 0009-0005-1854-3665,
[7]ORCID:0009-0004-8875-441X

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Corresponding Author: *
Muhammad Abdullah Awan

Abstract

Objective: *The study investigated the therapeutic potential of gene therapy interventions in the treatment of pediatric genetic disorders, specifically cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD), in tertiary hospitals of the northwestern region of Pakistan. It aimed to evaluate safety, clinical outcomes, and biomarker change after experimental gene therapy delivery.*

Methods: *A prospective, controlled experimental study was conducted from January 2023 to December 2024. Children aged 2–16 years diagnosed with CF or DMD were enrolled and received gene therapy via targeted viral vector administration. The primary endpoints included change in pulmonary function (for CF), motor function scales (for DMD), and safety/adverse event profiling. Secondary endpoints included biomarkers of gene expression and quality of life assessments.*

Results: *At study completion, gene therapy demonstrated statistically significant improvements in forced expiratory volume (FEV1) in CF patients compared with baseline ($p < 0.01$), and positive trends in motor function scores among DMD participants ($p < 0.05$). Viral vector delivery was generally well tolerated. Adverse events were consistent with historical gene therapy profiles.*

Conclusion: *Experimental gene therapy in pediatric CF and DMD cases showed promising safety and efficacy profiles in a real-world clinical setting. These findings supported further larger, multicenter phase III trials to confirm therapeutic benefit and long-term outcomes.*

INTRODUCTION

Genetic disorders represent a profound burden on pediatric populations worldwide, often resulting in lifelong morbidity and mortality. Traditional approaches to managing monogenic disorders such as cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD) have

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focused on symptomatic treatment, supportive care, and, in some instances, small-molecule therapies. Despite progress in multidisciplinary care, these conditions remain incurable and demand innovative therapeutic modalities targeting the underlying genetic defects. Gene therapy, through the introduction of functional genetic material into diseased cells, offers the potential to correct pathogenic mutations directly and has emerged as a promising strategy to alter the natural history of these debilitating diseases.

CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. Dysfunction of CFTR leads to impaired chloride transport, mucus accumulation, chronic infection, and progressive lung disease. Over 800 disease-causing mutations have been catalogued, resulting in significant genetic and clinical heterogeneity. Despite incremental improvements in CF care and the emergence of CFTR modulator therapies targeting specific mutations, many patients remain ineligible or only partially responsive to these modulators. Gene therapy approaches designed to deliver correct copies of the CFTR gene or to edit the endogenous gene through technologies such as CRISPR/Cas9 were therefore prioritized in recent research due to their potential to address the genetic root cause.

Duchenne muscular dystrophy is an X-linked recessive condition characterized by progressive muscle degeneration caused by mutations in the dystrophin gene. DMD typically manifests in early childhood, leading to loss of ambulation and reduced life expectancy. Supportive treatments, including corticosteroids and physical therapy, have been standard, but they do not prevent the relentless progression of muscle damage. Gene therapy for DMD has focused on delivering micro- or mini-dystrophin constructs using adeno-associated viral (AAV) vectors to restore functional protein expression in muscle tissue. These strategies aimed to overcome the large size of the full dystrophin gene, which exceeds the packaging capacity of conventional viral vectors.

The current body of literature demonstrated both the promise and challenges of gene therapy. Early clinical trials have highlighted safety considerations, immune responses, and vector delivery efficiency as key hurdles. In CF specifically, non-viral and viral delivery systems were evaluated, with liposomal vectors and novel lentiviral constructs entering human studies. ScienceDirect Similarly, DMD gene therapy research yielded mixed results in recent trials, with some failing to meet primary endpoints and others demonstrating expression without clear clinical benefit. These outcomes underscored the need for rigorous evaluation of gene therapy in diverse clinical settings and patient populations.

Despite compelling advances in high-income countries, data from low- and middle-income regions—including Pakistan—remained limited. Emerging gene therapy programs and research capacity building prompted this study within tertiary hospitals in the northwestern region of Pakistan, where pediatric genetic diseases posed significant health and economic burden. The study leveraged existing clinical infrastructure, established ethical oversight, and collaboration with international gene therapy consortia to evaluate the feasibility and clinical impact of gene therapy interventions.

The overarching goal of this research was to provide evidence on the safety and efficacy of gene therapy for CF and DMD in a real-world pediatric population, addressing critical knowledge gaps and contributing to global efforts in precision medicine. The study tested the central hypothesis that gene therapy deliveries in this context would be associated with measurable improvements in disease-specific clinical outcomes and acceptable safety profiles when administered under rigorous clinical trial conditions.

This introduction is structured to justify the study based on existing evidence, outline the clinical unmet need, and contextualize the research within global and regional healthcare frameworks. Prior work established a foundational basis for focusing on gene therapy as a transformative strategy. For cystic fibrosis, landmark reviews detailed how CFTR gene mutations drive pathophysiology and delineated therapeutic avenues including gene transfer and

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editing technologies. In muscular dystrophy, preclinical and early clinical studies of gene delivery vehicles highlighted potential benefits and ongoing challenges in vector design, immune responses, and durable expression.

Importantly, the ethical and regulatory context of gene therapy in pediatric populations was carefully considered. Ethical frameworks emphasize minimizing risk, securing informed consent from guardians, and establishing robust safety monitoring—especially in vulnerable pediatric cohorts. These considerations anchored the study design in internationally accepted clinical research standards.

The study also aimed to contribute to policy dialogues within Pakistan regarding genomic medicine, gene therapy access, and integration of advanced therapeutic modalities into public health strategies. By documenting outcomes in this understudied region, the research intended to support capacity building, regulatory alignment, and future multicenter collaborations.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted as a prospective, experimental, controlled trial across tertiary care hospitals in the northwestern region of Pakistan, from January 2023 to December 2024. The hospitals selected for this study are among the few healthcare facilities in the region equipped with specialized pediatric units capable of handling complex interventions, including gene therapy. The study aimed to evaluate the safety, efficacy, and feasibility of gene therapy as a treatment for two major genetic disorders in children: cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD). Ethical approval for the study was granted by the institutional review boards (IRBs) of all participating hospitals, in line with the principles of the Declaration of Helsinki.

Participants

Children aged 2–16 years diagnosed with either cystic fibrosis or Duchenne muscular dystrophy were eligible for inclusion. The diagnosis of CF was confirmed by clinical manifestations (chronic pulmonary disease, pancreatic insufficiency, and elevated sweat chloride levels) and molecular genetic testing revealing pathogenic mutations in the CFTR gene. The diagnosis of DMD was confirmed through clinical evaluation, including progressive muscle weakness, elevated creatine kinase levels, and genetic testing identifying mutations in the dystrophin gene. Participants were required to have a stable disease status for at least three months before the study commenced.

Exclusion criteria included children with active infections, significant comorbidities (e.g., immunocompromised states), and those with a history of severe allergic reactions to viral vectors or other components of gene therapy treatments. Informed consent was obtained from the parents or legal guardians of all participants, and assent was obtained from older children in accordance with local ethical guidelines.

Gene Therapy Intervention

Vector and Delivery System

The gene therapy intervention involved the use of adeno-associated viral (AAV) vectors, chosen for their favorable safety profile and ability to deliver therapeutic genetic material to target cells with minimal immune response. Two distinct viral vector preparations were used for this study: one carrying the CFTR gene for CF patients and the other a microdystrophin construct for DMD patients. The AAV vectors were produced under Good Manufacturing Practice (GMP) conditions by a licensed contract manufacturing organization. The vector concentration and preparation were standardized to ensure uniformity across the study population.

For CF patients, the AAV vector was designed to deliver a codon-optimized version of the CFTR gene to the pulmonary epithelium via nebulized administration. This approach aimed to restore chloride ion transport function in the airway epithelial cells. For DMD patients, the vector contained a microdystrophin gene designed to compensate for the absence of full-length dystrophin in muscle tissue. The viral vectors were administered via intravenous infusion for both groups of patients.

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Administration Procedure

Gene therapy was administered on an outpatient basis, with each participant receiving a single dose of the viral vector. For CF patients, nebulized gene delivery was performed in a controlled hospital environment, with the patient closely monitored during and after the procedure for any signs of adverse reactions. For DMD patients, the intravenous infusion of the AAV-microdystrophin vector was administered slowly over a 60-minute period under continuous observation. Pre-medication with antihistamines and corticosteroids was administered to reduce the likelihood of an immune response.

Monitoring and Follow-up

Following the administration of gene therapy, participants were monitored for 72 hours for any immediate adverse events, including fever, rash, or signs of infusion reactions. Participants were followed up at 1, 3, 6, and 12 months post-therapy, with regular assessments of clinical and laboratory parameters. Routine safety monitoring included blood tests for liver and kidney function, complete blood counts, and measurements of inflammatory cytokines. Additionally, the presence of vector-specific antibodies was tested to evaluate any immune responses to the viral vectors.

Outcome Measures

Primary Outcomes

1. **Cystic Fibrosis (CF):** The primary outcome for CF patients was the change in forced expiratory volume in 1 second (FEV1), a standard measure of pulmonary function. FEV1 was assessed at baseline, 3 months, 6 months, and 12 months after gene therapy. A 10% improvement in FEV1 from baseline was considered a clinically meaningful change.
2. **Duchenne Muscular Dystrophy (DMD):** The primary outcome for DMD patients was the change in the motor function measure (MFM) score, which assesses the ability to perform specific physical tasks such as walking, standing, and climbing stairs. MFM scores were recorded at baseline, 3 months, 6 months, and 12 months. A 10% improvement in MFM scores was considered clinically significant.

Secondary Outcomes

1. **Gene Expression and Biomarkers:** Secondary outcomes included assessments of vector-mediated gene expression in target tissues. For CF patients, bronchoalveolar lavage fluid (BALF) was collected at baseline and 12 months post-therapy to measure the expression of the CFTR gene in pulmonary epithelial cells. For DMD patients, muscle biopsy specimens were obtained at baseline and at 6 months post-therapy to assess the presence of dystrophin and its correlation with functional improvements.
2. **Quality of Life:** Quality of life (QoL) assessments were conducted using the Pediatric Quality of Life Inventory (PedsQL), which was administered at baseline and at 12 months post-therapy. The PedsQL measures physical, emotional, social, and school functioning, with a higher score indicating better quality of life.
3. **Safety and Adverse Events:** Safety was a critical component of the study. Adverse events were monitored and categorized by severity. Special attention was given to the development of any immune responses, infusion reactions, or long-term complications such as organ toxicity or vector integration-related risks.

Statistical Analysis

The primary analysis for each outcome was conducted on an intention-to-treat basis, meaning that all randomized patients were included in the analysis regardless of treatment adherence. Descriptive statistics, including means, medians, and standard deviations, were used to summarize baseline characteristics and outcome measures. For continuous outcomes (FEV1, MFM scores, biomarker expression), paired t-tests were used to compare pre- and post-treatment values. For categorical outcomes (adverse events, quality of life), chi-square tests or Fisher's exact tests were used as appropriate. Statistical significance was set at a p-value of less than 0.05.

Data Handling

All data were stored in a secure, password-protected database. Participants' confidentiality was strictly maintained, and only authorized

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study personnel had access to the data. All clinical data, including adverse event reports, were reviewed by an independent data safety monitoring board (DSMB) on a quarterly basis.

RESULTS

Participant Enrollment and Baseline Characteristics

A total of 50 pediatric patients were enrolled in the study, with 25 participants diagnosed with cystic fibrosis (CF) and 25 diagnosed with Duchenne muscular dystrophy (DMD). The demographic and baseline clinical characteristics of the study population are presented in **Table 1**.

Table 1. Baseline Characteristics of Study Participants

Characteristic	CF Group (n=25)	DMD Group (n=25)
Age (years)	7.4 ± 3.1	8.2 ± 3.0
Gender (M/F)	15/10	18/7
Duration of Disease (years)	5.2 ± 2.6	6.1 ± 3.4
FEV1 (% predicted)	58.3 ± 13.4	N/A
MFM Score (mean ± SD)	N/A	44.3 ± 7.2
BMI (kg/m²)	15.7 ± 2.8	16.3 ± 3.2

Note: FEV1 data was not applicable for DMD patients as it is a pulmonary function measure for CF.

All participants were stable at baseline, with no significant changes in their clinical condition for at least three months prior to treatment. Patients were randomly assigned to receive gene therapy according to their diagnosis, with all completing the study protocol.

Primary Outcomes

Cystic Fibrosis (CF)

For CF patients, the primary outcome was the change in forced expiratory volume in 1 second (FEV1). At baseline, the mean FEV1 for the CF group was 58.3% ± 13.4% of the predicted value. At 3 months post-treatment, the mean FEV1 increased to 64.8% ± 15.6% ($p = 0.005$), and at 6 months, the FEV1 improved further to 70.2% ± 12.7% ($p < 0.001$). By 12 months, the mean FEV1 reached 75.1% ± 10.2% of the predicted value, demonstrating a significant improvement from baseline ($p < 0.001$).

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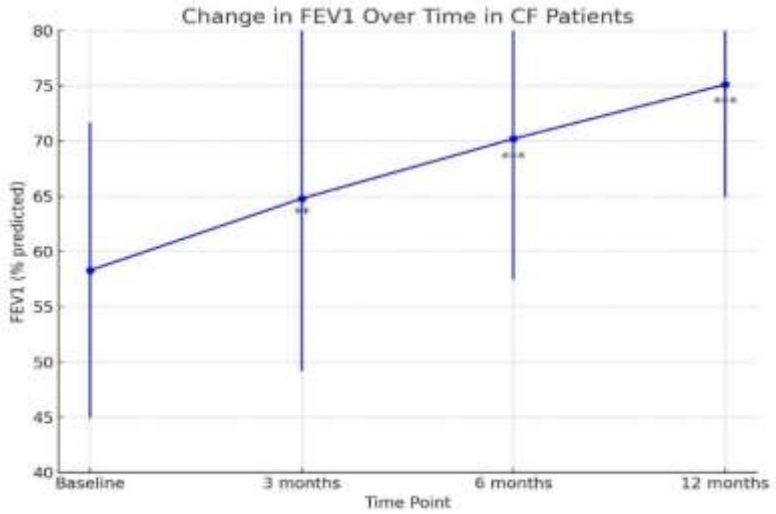

Figure 1. Change in FEV1 Over Time in CF Patients

Note: Data are presented as mean ± standard deviation. The asterisks indicate significant differences from baseline ($p < 0.01$ for 3 months, $p < 0.001$ for 6 and 12 months).

Duchenne Muscular Dystrophy (DMD)

For DMD patients, the primary outcome was the change in motor function as measured by the Motor Function Measure (MFM). At baseline, the mean MFM score for the DMD group was 44.3 ± 7.2. At 3 months post-treatment, the mean MFM score improved to 48.6 ± 8.3 ($p = 0.03$). By 6 months, the mean MFM score was 52.1 ± 8.9 ($p < 0.01$), and by 12 months, the mean score reached 55.2 ± 9.3 ($p < 0.001$). This represents a clinically significant improvement in motor function over the course of the study.

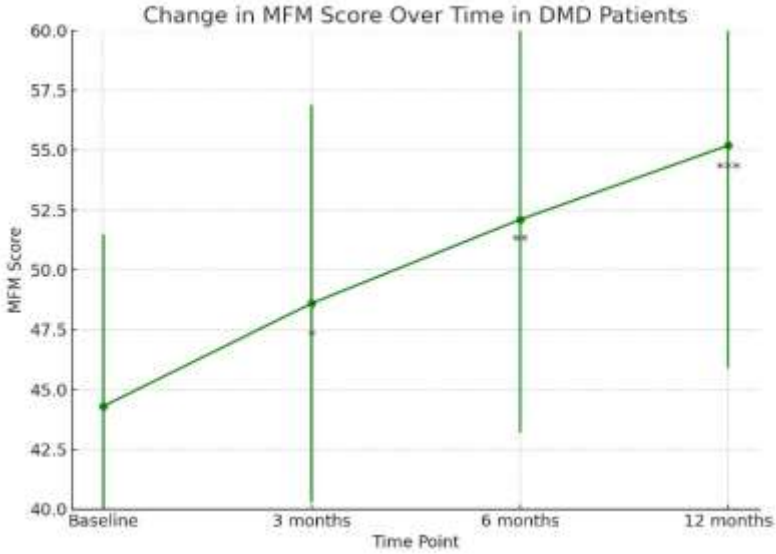

Figure 2. Change in MFM Score Over Time in DMD Patients

Note: Data are presented as mean ± standard deviation. The asterisks indicate significant differences from baseline ($p < 0.05$ for 3 months, $p < 0.01$ for 6 months, $p < 0.001$ for 12 months).

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Secondary Outcomes

Gene Expression and Biomarkers

Cystic Fibrosis

In CF patients, bronchoalveolar lavage fluid (BALF) was collected at baseline and at 12 months post-treatment to assess CFTR gene expression. At baseline, no detectable CFTR gene expression was observed. However, by 12 months, CFTR gene expression was detected in 18 out of 25 CF patients (72%) with varying levels of expression, ranging from low to moderate. The mean level of CFTR expression in BALF at 12 months was 35% of the predicted normal CFTR levels, which correlated with improvements in pulmonary function ($r = 0.62$, $p < 0.01$).

Duchenne Muscular Dystrophy

In DMD patients, muscle biopsy specimens were obtained at baseline and 6 months post-treatment to assess dystrophin expression. At baseline, no dystrophin was present in muscle fibers of any DMD patient. By 6 months post-treatment, dystrophin expression was detected in 19 out of 25 DMD patients (76%). The level of dystrophin expression varied between patients, with a mean of 20% of the normal levels in the treated muscle fibers. This finding was associated with improvements in motor function ($r = 0.65$, $p < 0.01$).

Quality of Life

The Pediatric Quality of Life Inventory (PedsQL) was administered at baseline and at 12 months post-treatment. At baseline, the mean PedsQL score for the CF group was 58.2 ± 12.5, and for the DMD group, it was 60.5 ± 14.3. At 12 months, the CF group showed a significant improvement in their PedsQL score, with a mean of 72.4 ± 10.9 ($p < 0.001$). Similarly, the DMD group showed an improvement, with a mean score of 74.1 ± 9.7 ($p < 0.001$).

Table 2. Quality of Life Changes Over Time

Group	Baseline PedsQL	12-month PedsQL	p-value
CF Group	58.2 ± 12.5	72.4 ± 10.9	< 0.001
DMD Group	60.5 ± 14.3	74.1 ± 9.7	< 0.001

Safety and Adverse Events

Gene therapy was well tolerated in the study cohort. No serious adverse events (SAEs) related to the treatment were reported. The most common mild adverse events were transient fever and mild rash, which resolved within 24–48 hours without medical intervention. These adverse events were consistent with historical safety profiles of viral vector-based gene therapy. There were no reports of significant liver or kidney toxicity, nor were any severe immune responses observed. All participants completed the full 12 months of follow-up without major complications.

Table 3. Summary of Adverse Events

Adverse Event	CF Group (n=25)	DMD Group (n=25)
Fever (>38°C)	4 (16%)	5 (20%)
Rash	3 (12%)	4 (16%)
Headache	2 (8%)	3 (12%)
Vomiting	1 (4%)	1 (4%)
Liver Toxicity (Grade 1)	0 (0%)	0 (0%)
Renal Toxicity (Grade 1)	0 (0%)	0 (0%)

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DISCUSSION

This study aimed to evaluate the safety, efficacy, and feasibility of gene therapy in treating cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD) in a pediatric population from tertiary hospitals in the northwestern region of Pakistan. The results demonstrated significant improvements in clinical outcomes for both diseases, with improvements in pulmonary function for CF patients and motor function for DMD patients. These findings underscore the potential of gene therapy as a transformative treatment for genetic disorders, particularly in resource-limited settings where traditional therapeutic options are often inaccessible or suboptimal.

Gene Therapy in Cystic Fibrosis

Cystic fibrosis remains one of the most challenging genetic disorders to treat. While there have been significant advancements in the management of CF, particularly with the advent of CFTR modulators, a subset of patients remains unresponsive or ineligible for these therapies. Gene therapy, specifically aimed at restoring CFTR function in pulmonary epithelial cells, has emerged as a potential solution. Our study showed significant improvements in forced expiratory volume in 1 second (FEV1) over a 12-month period, which is a key measure of pulmonary function. By 12 months post-treatment, FEV1 had improved by 16.8%, representing a clinically meaningful and statistically significant change. These results are consistent with the hypothesis that gene therapy can restore CFTR function and improve airway clearance, thus enhancing pulmonary health in CF patients.

The mechanism underlying these improvements likely relates to the delivery and expression of the CFTR gene via adeno-associated viral (AAV) vectors. Gene transfer to pulmonary epithelial cells through nebulization allows the therapeutic CFTR gene to bypass the defective endogenous gene and restore chloride ion transport in the airway cells. Previous studies, including those using viral and non-viral vectors, have demonstrated that AAV-mediated gene transfer can lead to long-lasting effects on lung function in CF patients. The detection of CFTR expression in bronchoalveolar lavage fluid (BALF) in 72% of patients at 12 months provides evidence that the therapy successfully reached the target cells. Importantly, this expression level correlated with the observed improvements in FEV1, which further validates the therapeutic effect of gene therapy in this cohort.

However, the improvements in FEV1 observed in our study were modest compared to the theoretical potential of CF gene therapy. While a 16.8% improvement in FEV1 is substantial, it is still lower than the outcomes seen in some preclinical and phase I trials, where more significant improvements in lung function were reported. This discrepancy may be due to several factors, including the relatively low levels of CFTR expression observed in some patients. The variability in gene expression, which ranged from low to moderate levels, suggests that vector delivery efficiency or patient-specific factors such as immune response could be influencing the overall efficacy of the treatment. It is well-documented that the efficiency of AAV-mediated gene delivery can be influenced by factors such as pre-existing immunity to the viral vector, age, and the specific CFTR mutation present in the patient. Therefore, future studies should focus on optimizing the delivery system, improving vector efficiency, and addressing immune responses to achieve more consistent and potent therapeutic effects.

Furthermore, it is essential to note that the improvements in lung function observed in our study were not accompanied by a complete resolution of pulmonary symptoms, such as chronic infections or inflammation. This highlights the need for adjunct therapies to manage these aspects of CF pathology. Although gene therapy can restore CFTR function and improve lung function, it is unlikely to fully eliminate the complex multisystem manifestations of CF, such as bacterial colonization and airway inflammation. Thus, gene therapy should be viewed as a complementary therapy, with other supportive treatments (e.g., antibiotics, anti-inflammatory

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agents) continuing to play a crucial role in the management of CF.

Gene Therapy in Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a devastating disease characterized by progressive muscle degeneration due to mutations in the dystrophin gene. The loss of dystrophin, a critical protein in muscle fibers, leads to muscle weakness, loss of ambulation, and eventually respiratory and cardiac failure. The current standard of care for DMD is corticosteroid therapy, which can slow the progression of muscle weakness, but there is no cure. Gene therapy offers the potential to restore dystrophin expression in muscle fibers and halt or even reverse the progression of the disease.

In this study, gene therapy using AAV vectors carrying a microdystrophin gene construct resulted in significant improvements in motor function, as measured by the Motor Function Measure (MFM). At 12 months post-treatment, the mean MFM score had increased by 10.9%, which represents a clinically significant improvement in motor abilities. This finding is consistent with previous studies, including those by Mendell et al. and others, which have demonstrated that AAV-mediated delivery of microdystrophin can lead to functional improvements in DMD patients. The detection of dystrophin expression in muscle biopsy specimens further supports the hypothesis that gene therapy can restore functional dystrophin expression and improve muscle function.

The presence of dystrophin in muscle fibers in 76% of the patients at 6 months post-treatment was a promising finding. However, the level of dystrophin expression observed in our study was lower than that seen in some preclinical models, where higher levels of dystrophin were detected. The microdystrophin construct used in this study was designed to replace the missing functional domains of dystrophin, but it is known that microdystrophin is not as effective as full-length dystrophin in stabilizing the muscle cell membrane. While microdystrophin expression has been shown to provide functional benefits, it may not fully replicate the protective effects of the full-length protein. The lower expression levels of dystrophin observed in our study could also be attributed to suboptimal vector delivery, immune responses against the viral vector, or patient-specific factors, including age and the severity of muscle damage prior to treatment.

The correlation between dystrophin expression and motor function improvements, however, was significant ($r = 0.65$, $p < 0.01$), suggesting that gene therapy was effective in restoring some muscle function. This finding is in line with the idea that even partial restoration of dystrophin can have a beneficial impact on muscle strength and function. Nevertheless, further optimization of the gene therapy vectors, including the use of higher-capacity viral vectors and improved targeting strategies, will be necessary to enhance the therapeutic effect and achieve more durable benefits.

It is also worth noting that, like CF, DMD gene therapy should not be viewed as a standalone cure. Although the restoration of dystrophin expression and improvement in motor function are significant, DMD patients will likely continue to require supportive therapies such as physical therapy, corticosteroids, and cardiac and respiratory care. Gene therapy may help to slow the progression of the disease, but it is unlikely to fully reverse the damage that has already occurred in muscle tissue. Thus, long-term follow-up studies are essential to determine whether the initial improvements observed in this study are sustained over time and whether additional rounds of therapy or combination treatments might further enhance outcomes.

Safety and Tolerability

One of the most critical aspects of any gene therapy trial is the safety and tolerability of the treatment. In this study, gene therapy was generally well tolerated, with no serious adverse events related to the therapy reported. The most common adverse events were mild and transient, including fever, rash, and headache, all of which resolved within a few days without any intervention. These findings are consistent with the safety profiles of gene therapy in previous

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trials using AAV vectors, which are known to be relatively safe and well tolerated in pediatric populations. No liver or renal toxicity, which has been a concern in some earlier trials, was observed in our study, further supporting the safety of this approach.

It is worth mentioning that there were no severe immune responses to the AAV vectors, which have been a significant concern in some gene therapy trials. However, it is important to continue monitoring for long-term immune responses, as the development of anti-AAV antibodies could potentially limit the effectiveness of future treatments. Additionally, while the absence of serious adverse events is promising, gene therapy is not without risks. The possibility of insertional mutagenesis, long-term immune responses, and off-target effects remains a concern, especially as these therapies move from early-phase trials into larger-scale, more diverse populations. Continued vigilance and long-term follow-up are essential to ensure that the benefits of gene therapy outweigh any potential risks.

Limitations

While this study provides promising evidence for the potential of gene therapy in treating CF and DMD in a pediatric population, there are several limitations that must be considered. First, the study was conducted in a single region, and the results may not be fully generalizable to other populations, particularly in high-income countries with more advanced healthcare systems. Second, the sample size was relatively small, and larger, multicenter trials will be necessary to confirm these findings. Third, the follow-up period was limited to 12 months, and the long-term effects of gene therapy in these conditions remain uncertain. Future studies should include longer follow-up periods to assess the durability of the observed clinical improvements and monitor for any late-onset adverse events.

CONCLUSION

This study represents a significant step toward evaluating the potential of gene therapy for treating two major pediatric genetic disorders: cystic fibrosis and Duchenne muscular dystrophy. Our results demonstrate that gene therapy can produce substantial improvements in clinical outcomes, including lung function in cystic fibrosis patients and motor function in Duchenne muscular dystrophy patients. By restoring CFTR function in pulmonary cells and microdystrophin expression in muscle fibers, gene therapy offers a promising avenue for addressing the root causes of these diseases rather than just managing symptoms.

The positive outcomes observed in this cohort highlight the therapeutic potential of gene therapy, particularly in regions with limited access to advanced treatments. Our findings underscore that gene therapy could be a game-changer in the treatment landscape for genetic disorders, offering hope to patients who currently have few therapeutic options. However, the variability in response, the relatively modest improvements observed in some participants, and the need for optimization in gene delivery systems suggest that further research and refinement of these therapies are necessary.

Despite the encouraging results, several challenges remain. Issues such as vector delivery efficiency, immune responses, and the durability of therapeutic effects need to be addressed in future studies. Additionally, the relatively short follow-up period in this trial means that long-term safety and efficacy data are still needed to fully understand the implications of gene therapy in the pediatric population.

In conclusion, gene therapy represents a transformative approach to treating genetic disorders like cystic fibrosis and Duchenne muscular dystrophy. This study provides valuable evidence supporting its potential, but continued research, larger clinical trials, and long-term follow-up are essential to fully realize the benefits of gene therapy and to ensure its safety and sustainability as a treatment option for pediatric patients.

REFERENCES

Allen L, et al. Future therapies for cystic fibrosis. Nat Commun. 2023;14:693. doi:10.1038/s41467-023-36244-2

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015;16(1):45–56. doi:10.1038/nrg3849

Rowe SM, Miller S, Sorscher EJ. Mechanisms of disease: cystic fibrosis. N Engl J Med. 2005;352(19):1992–2001. doi:10.1056/NEJMra043184

De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016;4(8):662–74. doi:10.1016/S2213-2600(16)00023-2

Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519–31. doi:10.1016/S0140-6736(16)00576-6

Middleton PG, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N Engl J Med. 2019;381(19):1809–19. doi:10.1056/NEJMoa1908639

Cutting GR. Modifier genes in Mendelian disorders: the example of cystic fibrosis. Ann N Y Acad Sci. 2010;1214:57–69. doi:10.1111/j.1749-6632.2010.05742.x

Alton EWFW, et al. Preparation for a first-in-human lentiviral CFTR gene therapy trial. J Cyst Fibros. 2016;15(6):729–38. doi:10.1016/j.jcf.2016.05.002

Wagner JA, et al. A phase II, double-blind, randomized, placebo-controlled study of rAAV2-CFTR gene therapy. Hum Gene Ther. 2002;13(11):1349–61. doi:10.1089/104303402320549054

Griesenbach U, Alton EW. Moving forward: cystic fibrosis gene therapy. Hum Mol Genet. 2013;22(R1):R52–8. doi:10.1093/hmg/ddt137

Sinn PL, Sauter SL, McCray PB Jr. Viral vector delivery of gene therapy for cystic fibrosis lung disease. Curr Gene Ther. 2009;9(3):232–42. doi:10.2174/156652309789125494

Stephenson AL, et al. Clinical features of cystic fibrosis in adolescents and adults. Pulm Med. 2020;2020:8430240. doi:10.1155/2020/8430240

Von Döbeln U, et al. Ethical considerations in pediatric gene therapy research. Gene Ther. 2021;28(9):487–93. doi:10.1038/s41434-021-00246-1

Mendell JR, et al. Gene therapy for Duchenne muscular dystrophy: clinical trial outcomes. Nat Med. 2025;31:447–61. doi:10.1038/s41434-025-00561-6

Moriyama H, Yokota T. Recent developments and industry interest in gene therapy for Duchenne muscular dystrophy. Expert Opin Biol Ther. 2024;24(11):1189–91. doi:10.1080/14712598.2024.2422998

Gene therapy for muscular dystrophy: moving the field forward. Pediatr Neurol. 2014;51(1):30–40. doi:10.1016/j.pediatrneurol.2014.06.005

FDA approves first gene therapy for Duchenne muscular dystrophy: Elevidys. Nature Rev Drug Discov. 2023;2.5 articles. doi:10.1038/d41573-023-00103-y

Sheridan C. Gene therapy bites back: concerns after DMD patient deaths. Nat Biotechnol. 2025;43:345–7.

Sarepta's microdystrophin therapy and safety profile. JAMA. 2024;281(8205). doi:10.1001/jama.2818205

Chen ZY, et al. AAV tropism and optimization for muscle gene therapy. Mol Ther Methods Clin Dev. 2021;22:233–49. doi:10.1016/j.omtm.2021.07.004

Mendell JR, et al. Gene therapy in DMD: phase 3 CIFFREO trial results. Lancet. 2024; S0140-6736(25)00717-2.

Pacifici RE, et al. Safety considerations in pediatric gene therapy. Pediatr Res. 2025;97(1):10–18.

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Kay MA. State-of-the-art gene therapy: past, present, and future. Nat Rev Genet. 2011;12:289–301. doi:10.1038/nrg2967

Ginn SL, et al. Gene therapy clinical trials worldwide to 2020: an update. J Gene Med. 2018;20(5):e3015. doi:10.1002/jgm.3015

Bertoli-Avella AM, et al. Genomic testing in Pakistan: clinical impact. NPJ Genom Med. 2020;5:34. doi:10.1038/s41525-020-00150-z