

Gene Therapy Strategies and Clinical Management in Duchenne Muscular Dystrophy

Rafael Domingues*

Department of Medical Genetics, University of Porto, Porto, Portugal

DESCRIPTION

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder characterized by progressive muscle degeneration resulting from mutations in the *DMD* gene, which encodes dystrophin. This protein plays a vital role in maintaining the structural stability of muscle fibers by linking the cytoskeleton to the extracellular matrix. The absence or severe reduction of dystrophin leads to muscle fragility, repeated cycles of damage and repair, and eventual replacement of muscle tissue with fat and fibrosis. The condition typically presents in early childhood, often before the age of five, with delayed motor milestones, difficulty running, and frequent falls. Affected individuals may exhibit Gowers' sign, using their hands to push themselves upright from a seated position. As the disease progresses, muscle weakness becomes more pronounced, eventually affecting respiratory and cardiac muscles. Without intervention, many patients lose ambulation during adolescence.

At the molecular level, *DMD* is caused by deletions, duplications, or point mutations in the dystrophin gene located on the X chromosome. These mutations disrupt the reading frame, leading to the production of a nonfunctional protein. Advances in molecular diagnostics, including multiplex ligation-dependent probe amplification and next-generation sequencing, have enabled precise identification of mutation types, which is essential for selecting appropriate therapeutic strategies. One of the most significant developments in *DMD* research is the exploration of gene-based therapies. Exon skipping is a technique that uses antisense oligonucleotides to modify pre-mRNA splicing. By skipping specific exons, the reading frame can be restored, allowing the production of a shorter but partially functional dystrophin protein. This approach has shown clinical benefit in subsets of patients with amenable mutations and represents an important step toward personalized treatment.

Another strategy involves the use of viral vectors to deliver micro-dystrophin genes. Due to the large size of the dystrophin gene, full-length delivery is challenging. Micro-dystrophin constructs are engineered to retain essential functional domains while

being small enough for packaging into adeno-associated viruses. Early clinical trials have demonstrated improved muscle function and increased dystrophin expression, although long-term efficacy and safety continue to be evaluated. Genome editing technologies, particularly Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas systems, are also being investigated as potential treatments. These approaches aim to correct mutations directly at the Deoxyribonucleic acid (DNA) level, offering the possibility of a more permanent solution. Preclinical studies have shown encouraging results, with restoration of dystrophin expression in animal models. However, challenges related to delivery, off-target effects, and immune responses must be addressed before widespread clinical application.

In addition to gene therapy, pharmacological treatments play a role in managing *DMD*. Corticosteroids are commonly used to slow disease progression by reducing inflammation and stabilizing muscle membranes. While beneficial, long-term use is associated with side effects such as weight gain, bone fragility, and metabolic disturbances. Ongoing research is focused on developing alternative agents with improved safety profiles. Cardiac and respiratory care are critical components of disease management. Cardiomyopathy is a leading cause of morbidity, requiring regular monitoring and treatment with medications such as angiotensin-converting enzyme inhibitors and beta-blockers. Respiratory support, including non-invasive ventilation, can significantly extend life expectancy and improve quality of life.

The integration of multidisciplinary care has transformed outcomes for individuals with *DMD*. Coordinated management involving neurologists, cardiologists, pulmonologists, physiotherapists, and genetic counselors ensures comprehensive care. Early intervention and regular follow-up are essential for addressing complications and optimizing function. Ethical considerations are particularly relevant in the context of emerging gene therapies. Issues related to accessibility, cost, and long-term monitoring must be carefully considered. Informed consent is also complex, especially when treatments are administered to young children. Ensuring equitable access to

Correspondence to: Rafael Domingues, Department of Medical Genetics, University of Porto, Porto, Portugal, E-mail: rafael.domingues.genetherapy@upmed.pt

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advanced therapies remains a significant challenge for healthcare systems worldwide.

CONCLUSION

Duchenne muscular dystrophy represents a model condition for the application of gene therapy in inherited disorders. Advances in molecular genetics have led to the development of targeted treatments that address the underlying cause of the disease.

While challenges remain, ongoing research and clinical innovation are steadily improving outcomes and offering new possibilities for individuals affected by this condition. Research efforts continue to expand our understanding of *DMD* and its treatment. Biomarkers such as serum creatine kinase levels and imaging techniques like muscle Magnetic Resonance Imaging (MRI) are being refined to assess disease progression and therapeutic response. These tools are important for evaluating the effectiveness of new interventions in clinical trials.