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Editorial

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Duchenne muscular dystrophy: diagnosis and perspective of treatment

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Duchenne Muscular Dystrophy (DMD) is an X-linked genetic dystrophy characterized by progressive myofiber degeneration and weakness, as well as cardiac involvement including dilated cardiomyopathy and heart dilatation. As of 2024, DMD remains incurable, but significant progress has been made since the discovery of the dystrophin gene in 1986 by Monaco and the dystrophin protein by Eric Hoffmann. Clinical trials are crucial for advancing the understanding and treatment of DMD. This Special Issue focuses on advancements in Dystrophinopathies research. I would like to take this opportunity to invite you to submit your outstanding research achievements to the Special Issue "Genetic Diagnosis and Treatment of Duchenne Muscular Dystrophy" in *Journal of Translational Genetics and Genomics* (*JTGG*, Online ISSN: 2578-5281, indexed by Scopus, ESCI), an international open-access journal that conducts rigorous peer-review. This article highlights key developments in diagnosis, evolving treatments, and ongoing clinical trials.

The diagnosis of DMD typically involves a comprehensive clinical evaluation regarding clinical signs, gait initiation, genetic testing, and muscle biopsy, which mainly involves testing for creatine kinase (CK), hemopexin, myoglobin, Southern blot analysis, immunohistochemistry, multiplex PCR, multiplex ligation-dependent probe amplification, Sanger DNA sequencing, and next-generation DNA sequencing. Genetic testing confirms the diagnosis by identifying mutations in the dystrophin gene. Additionally, Western blotting and immunohistochemistry aid in diagnosing and differentiating between DMD, intermediate and

atypical cases, and Becker muscular dystrophy (BMD), as well as carriers. However, identifying appropriate primary outcomes and tools remains a challenge in DMD research. Tests such as the 6-minute walk test (6MWT), Gross Motor Function Measure (GMFM), North Star Ambulatory Assessment (NSAA), timed function tests, quality of life assessments, and daily activity monitoring have all been utilized but yield varying rates of success in trials.

Early indicators of DMD may include delayed motor milestones, with some children not walking until 18 months of age, muscle weakness, particularly in the pelvic muscles, enlarged calves, and gait abnormalities. Patients often exhibit a waddling gait and have difficulty rising from the floor, known as Gowers' sign.

Steroid therapy remains the cornerstone of treatment for DMD, regardless of the specific dystrophin gene variant in affected children. Corticosteroids, such as prednisone and deflazacort, are commonly used to slow the progression of muscle weakness in DMD. While disease-modifying therapies are emerging, they still present significant limitations and might be applicable only to selected groups of DMD patients with different pathogenic variants. These evolving treatments include exon-skipping drugs (e.g., eteplirsen, golodirsen) and gene therapies that are undergoing trials with promising outcomes.

Steroids are currently the only treatment proven to slow disease progression, despite significant advancements in other therapeutic strategies. However, long-term steroid use poses risks of adverse effects[1-3]. Gene editing using the CRISPR system is a promising therapeutic approach, along with other investigational treatments such as exon skipping therapy, microdystrophin therapy, stop codon readthrough therapy, and utrophin upregulation. However, challenges such as delivery efficiency, off-target mutagenesis, and long-term maintenance of dystrophin must be addressed. In particular, further studies focusing on the safety and accuracy of CRISPR are necessary before clinical translation. Overall, the latest advances in DMD treatment involve gene therapies, exon skipping, and gene or cellular therapies.

However, despite recent advances in translational research and general healthcare, DMD, a muscle-wasting disease, remains 100% fatal. Individuals born with Duchenne typically do not live beyond their mid-20s. Nevertheless, with multiple treatments now available, some are entering their fourth decade, marking a critical transition from childhood to adult cure, which presents a significant challenge. Developing a treatment, and ultimately a cure, is crucial. Apart from muscular dystrophy, bone loss is a prominent symptom of this genetic disorder. Bisphosphonates are commonly prescribed to address this issue in DMD patients. Choosing the appropriate therapy has demonstrated the potential to improve muscle dysfunction and prevent future bone loss.

Additionally, Dystrophinopathies, including DMD and Becker muscular dystrophy (BMD), are X-linked conditions resulting from out-of-frame or in-frame variants of the Dystrophin gene. A drug-modifying approach to treating DMD should decrease inflammation and fibrosis caused by dystrophin deficiency, and promote muscle satellite cell regeneration and their maturation into myofibers that might ultimately improve muscle strength and functional performance.

Remarkably, patients carrying the 1,220 A to G (Asn363Ser - N363S) polymorphism in the steroid receptor had longer deambulation[1] before becoming wheel-chair bound. This indicates a better steroid response in DMD patients, resulting in a more effective treatment profile. The efficacy of a novel steroid, deflazacort (DF), was assessed through a three-year, double-blind controlled trial, where DMD patients were treated with either deflazacort (DF) at 2.0 mg/kg every other day or a placebo. The DF group showed progress on the GSGC scale and remained ambulant for over a year, longer than the placebo group. DF has been used in

several DMD trials to evaluate the effects of different corticosteroid dosing regimens[3]. Through a detailed comparison, the FOR-DMD trial revealed a clear efficacy profile. In this trial, 164/196 randomized DMD boys were analyzed, showing better results with daily steroid treatment using either prednisone or DF, with the latter resulting in less weight gain.

Vamorolone is an innovative steroid that maintains efficacy while reducing metabolic side effects[4]. It has been approved for DMD, and clinical trials for BMD are ongoing. Recent advances in brain imaging have revealed abnormalities associated with dystrophinopathy, which have been linked to low IQ in one-third of DMD cases. In both DMD and BMD, cortical atrophy is associated with ventricular dilatation and changes in white matter appearance[5]. The myopathological mechanisms suggest that repeated cycles of myofiber degeneration exhaust the regenerative capacity of muscle satellite cells and macrophages induce fibrotic mechanisms, thereby causing progressive myofiber replacement with collagen. To counteract this, several approaches have been attempted, including the recent use of givinostat.

Eteplirsen, an antisense-oligonucleotide drug that induces exon 51 skipping, is available on the market. A recent study has shown improved overall survival[6] among the majority of US patients receiving eteplirsen since its approval, compared to a natural history cohort. Approximately 14% of DMD patients benefit from eteplirsen.

Ataluren is used to overcome stop codon mutations in DMD, including in female carriers. Nonsense mutations are present in about 14% of DMD cases. Ataluren (Translarna, PTC124) received conditional marketing approval in 2014, though its use was discussed by the EMA.

Regarding gene therapy for DMD, one major challenge is that the full DMD gene is too large to fit into an adeno-associated virus (AAV) vector, leading to the development of microdystrophin.

Fordadistrogene or movaparvovec is an investigational gene therapy utilizing a modified adeno-associated virus serotype 9 (AAV9) capsid to deliver a shortened, but functional dystrophin (mini-dystrophin) under the control of a human muscle-specific promoter. The virus is delivered into the blood via a single infusion. This treatment aims to slow or halt DMD muscle degeneration. The CIFFREO trial randomly assigned 226 ambulatory boys (nearly 2/3 of the participants) on a stable corticosteroid regimen to receive the gene therapy (at 200 trillion vector genomes per kg body weight) or a placebo. After a year, the boys who received fordadistrogene movaparvovec would get the placebo and boys first given the placebo would receive the gene therapy. The trial was paused following the sudden death of a boy who received the gene therapy.

The primary endpoint of the trial was to assess changes in motor skills using the North Star Ambulatory Assessment total score after one year. However, neither the gene therapy nor placebo groups showed statistically significant differences, nor did secondary endpoints such as the time needed for a 10-meter walk/run and rising from the floor (Gowers' sign).

Sarepta Therapeutics' Delandistrogene moxeparvovec (SRP-9001), another adeno-associated virus gene therapy designed to carry a "microdystrophin", has been approved for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD. However, continued approval is still to come, and pioneering research is ongoing in dystrophic muscle, with further trials anticipated.

Furthermore, managing effective follow-up and preventing contractures are important components of optimal care for DMD patients. Some DMD patients develop joint contractures; in such cases, optimal physiotherapy is beneficial over surgical interventions. Newer treatments, such as deflazacort or vamorolone, week-end regimens, are also used to accommodate caregivers and families.

Additionally, many clinicians recommend continuing glucocorticoid therapy even after the loss of ambulation, while others prefer discontinuing it if the patient is wheelchair-bound. Treatment should be initiated before any physical decline is observed and after thorough family discussions and planning[7-8]. This planning should involve dietary advice, blood tests, and consideration of possible side effects[9].

The benefits of steroid treatment are more significant with early initiation, which requires an early diagnosis to prevent cardio-respiratory complications from bracing and overnight ventilators.

The involvement of skeletal and cardiac muscles does not occur simultaneously, but treatment at both levels is necessary. With the use of assisted ventilation, spinal surgery, and cardiomyopathy management through drugs, DMD patients can survive up to 40 years.

Regarding Becker muscular dystrophy, which presents with a heterogeneous clinical profile, its treatment is under investigation[10]. Notably, heart transplants have been performed for both DMD and BMD patients. Recent progress in the dystrophinopathy field has been remarkable, and we commend all researchers for their significant contributions to the field of DMD. I sincerely invite these pioneer scientists to contribute to a Special Issue of the journal *JTGG*, which maintains rigorous peer-review standards.

The socioeconomic impact of these disorders is profound, affecting the quality of life and daily activities of individuals, families and caregivers. Academic achievements in Dystrophinopathy are widely recognized for their substantial societal and media impact, as well as their engagement with Patient Associations. Once again, I express my gratitude to researchers for their contributions to Dystrophinopathy research and invite submissions of case reports, reviews, or exceptional translational research.

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