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GENE THERAPY FOR DUCHENNE MUSCULAR DYSTROPHY: A NEW HOPE?

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Duchenne muscular dystrophy (DMD) is a severe genetic disorder caused by the absence of the dystrophin protein, leading to progressive muscle weakness and degeneration. In June 2023, the Food and Drug Administration (FDA) approved a novel gene therapy named "ELEVIDYS®" for the treatment of DMD, offering new hope for patients previously deemed untreatable.

The pathophysiology of DMD involves mutations in the DMD gene that forms dystrophin, a crucial structural protein in several tissues, resulting in its decrease or absence. The deficiency or absence thereof in muscle tissue results it in being more susceptible to damage leading to necrosis and replacement with connective and adipose tissue. Clinically, DMD manifests with symptoms such as delayed motor milestones, muscle weakness, and musculoskeletal abnormalities, as well as cardiomyopathy and respiratory issues.

The individualized treatment plan for the patient can be aimed at restoring dystrophin or managing the secondary effects of the absence or lack of dystrophin. In the vein of the former, the promising gene therapy ELEVIDYS® (delandistrongene moxeparvovec-rokl) utilizes an adeno-associated virus vector (AAVrh74) to deliver a transgene that produces micro-dystrophin, which localizes to the sarcolemma. Additionally, a muscle-specific promoter regulating the activity of the MHCK7 gene is delivered.

The multiple clinical trials conducted on ELEVIDYS® show significant improvements in functional performance of patients and increased production of dystrophin in muscle tissue compared to placebo groups, as well as good tolerability and a safety profile. The method has the additional advantage of being a one-time subcutaneous injection. However, limitations on usage to ambulatory paediatric patients aged 4 to 5 years with confirmed genetic mutations and the contraindication in cases involving exon 8 and/or 9 defects are drawbacks. A global randomized, double-blind, phase III clinical trial (EMBARK) including patients from of a larger range of ages (4-7 years), revealed the results of North Star Ambulatory Assessment (NSAA) scores to improve by 2.6 points, although not being significantly different from the placebo group, demonstrated the possible applicability to a wider range of ages.

Side effects of the treatment range from mild, such as nausea, vomiting and pyrexia to severe, such as immune-mediated myositis and myocarditis. There exists a possibility of treatment failure if the patient has pre-existing anti-AAVrh74 antibodies. Therefore, for the usage of ELEVIDYS® in the clinical setting, it is important to have appropriate diagnostic methods as well as stringent follow-up after infusion.

Overall, ELEVIDYS® represents a promising advancement in DMD treatment, with potential applications for other mutations in the future, and the prospect of the combined therapy with other methods of gene therapy. Further research into expanding the applicability of the treatment to more age group and including non-ambulatory patients further, while simultaneously reducing the adverse effects needs to be performed. Nevertheless, as a stepping stone into the future, ELEVIDYS® offers hope for a shift from only symptomatic therapy to the pathogenetic treatment of DMD.