I. Updates on solutions to DMD

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Duchenne muscular dystrophy (DMD), an X-linked recessive condition, is estimated to affect 19.8 per 100,000 males worldwide at birth. The most prevalent type of DMD affects children and is brought on by mutations in the DMD gene that cause low or nonexistent amounts of the functioning cytoskeletal protein dystrophin. Progressive muscular injury and degeneration are caused by this underlying pathophysiology, which ultimately leads to early mortality [1].

A number of radical approaches, including gene therapy and stem cell transplantation, have been researched recently due to the obvious need for better disease-modifying treatments for DMD. Researchers and medical professionals working with DMD are particularly interested in exon-skipping therapy, which uses sequence-specific antisense oligonucleotides (ASOs) to cause an in-frame mutation in mature messenger RNA (mRNA).

The Food and Drug Administration (FDA) in the US approved the exon 51-skipping ASO eteplirsen (Exondys 51) for the treatment of DMD patients in 2016. However, the European Medicines Agency has not yet approved it for use in Europe. The FDA approved the exon 53-skipping ASO golodirsen (Vyondys 53) in 2019. Another exon 53-skipping ASO, Viltolarsen (NS-065/NCNP-01; Viltelpso), received FDA and Japanese Pharmaceuticals and Medical Devices Agency approval in 2020 [1].

The National Centre of Neurology and Psychiatry (NCNP) in conjunction with Nippon Shinyaku Co., Ltd. discovered and created Viltolarsen (NS-065/NCNP-01). This morpholino oligomer was discovered in preclinical experiments to induce exon 53 skipping in a dose-dependent manner and to increase dystrophin protein levels in patient-derived cells. Early-stage clinical development of NS-065/NCNP-01 started in 2016, with the hope that it would help the 6%–9.4% of DMD patients who were receptive to exon 53 skipping based on the documented locations of mutations in the DMD gene. In 2020, the FDA gave viltolarsen conditional approval pending the results of the ongoing phase III RACER53 trial, based on encouraging phase II data [2].
II. Outcome of a clinical study in DMD with immune-modulating beta-glucans

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The first diagnosis of DMD was made over 150 years ago but the first World Duchenne Awareness Day was celebrated in 2014, started by Elizabeth Vroom and Nicoletta Madia of the World Duchenne Organization [3]. 

Duchenne muscular dystrophy (DMD) constitutes one of the four muscular conditions called dystrophinopathies. The other three being Becker Muscular dystrophy (BMD, a mild form of DMD); an intermediate clinical presentation between DMD and BMD; and DMD-associated dilated cardiomyopathy (heart-disease) with little or no clinical skeletal, or voluntary, muscle disease [4]. DMD is a genetic disorder in which there is progressive muscle degeneration and weakness due to the mutations of the gene that produces a protein called dystrophin that helps keep muscle cells intact. 1 in 5000 boys are affected by DMD. Girls can also be carriers of this disease but are only mildly affected. DMD has no cure. The major mode of therapy has been muscle strengthening exercises and corticosteroid therapy. Gene replacement and exon-skipping therapies to correct the mutations in dystrophin gene are being experimented upon [3].

The involvement of Nichi-In Centre for Regenerative Medicine (NCRM) and its sister concern GN Corporation, Japan in DMD started in 2010 with research on biological response modifier glucans (BRMGs) [4]. The origin of BRMGs goes back to 1980s when Prof. Noboru Fujii of Miyazaki University discovered a specific strain of a poly extremo-tolerant black yeast Aureobasidium pullulans which secretes a novel exo-polysaccharide Beta 1,3-16 glucans with potent BRMG activities [4]. This production was then scaled up from lab-scale to industrial scale in GMP apart from continued research yielding multiple strains with unique produce. The AFO-202 beta glucan produce has been reported to have metabolic balancing potential with regulation of blood glucose [5,6] apart from immune enhancement while N-163 beta glucan had abilities to balance the lipid profile, anti-inflammatory properties and immunomodulation [7] which GNC and NCRM upon proving with several basic, and pre-clinical studies [8,9] undertook a clinical study in young adults with DMD yielding a path breaking outcome [10]. The study [10] showed that supplementation with N-163 strain produced beta glucan led to a significant decrease in inflammation and fibrosis markers, IL-6, IL-13 and TGF-β apart from increase in blood plasma Dystrophin levels and muscle strength improvement.

The increase in blood plasma dystrophin led us to study the implications. There has been increasingly strong emerging evidence that the primary cause of DMD is a lack of dystrophin in the smooth muscle of blood vessels and not the skeletal or cardiac muscle, as believed for long. The restricted blood supply results in muscle ischemia, injury and fatigue during exercise which leads to fibrosis and progressive muscle damage [11,12]. The beta glucans capable of modulating vascular pathology by angiogenesis promotion, decreasing atherosclerosis by positive effects on lipid metabolism, PPAR agonist action and immune-modulation apart from beneficially modulating the gut bacteria [13] thus helping on a systemic scale via the gut microbiome-brain axis thus can be an effective and affordable solution to children with DMD and muscular dystrophies until a full blown effective gene therapy is developed after which it can serve as an effective adjunct.
References


