Newer advances in the treatment of Duchenne muscular dystrophy and spinal muscular atrophy

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INTRODUCTION

The field of inherited neuromuscular disorders has been revolutionized due to strides made by genetics which has provided immense insight into the underlying disease pathophysiology. Last decade is witness to newer therapeutic options for many inherited neuromuscular disorders. We are summarizing here the recent advances in therapeutic options for two common inherited neuromuscular disorders, Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA).

DUCHENNE MUSCULAR DYSTROPHY

Dystrophinopathies are a group of devastating diseases encompassing a spectrum of rare, progressive, X-linked, recessive, and muscle-wasting disease ranging from mild to severe, which includes DMD, Becker muscular dystrophy (BMD), and DMD-associated dilated cardiomyopathy. Dystrophinopathies arise due to mutations in the dystrophin gene which is responsible for encoding dystrophin, a homonymous protein located primarily in skeletal and cardiac muscles. While the “out of frame” deletions disrupt translation and cause near-complete inactivation which leads to DMD, the “IN-frame” mutations lead to truncated but partly functional dystrophin protein causing BMD. Patients with DMD have <3% dystrophin levels whereas even severe forms of BMD have 5%–20% of dystrophin levels. Majority of DMD cases are due to large deletions (69%) in the DMD
gene that disrupt the normal transcript. Large duplications account for 11% cases, while the nonsense, missense and intronic mutations represent 20% of the cases. DMD has high de novo mutation rate (1 in 3).

Current therapeutics in DMD falls in two categories [Table 1]:
1. Target the primary defect – dystrophin
2. Target downstream pathophysiological mechanisms.

**RECTIFYING THE PRIMARY DEFECT: RESTORING DYSTROPHIN PROTEIN**

**Nonsense suppression**
Ataluren is an oral drug used for genetic disorders caused by Nonsense mutations. Premature stop codon interrupts protein synthesis and ataluren enables ribosomal read through at these premature stop codons. This results in full translation of mRNA and production of entire protein. Around 10%–15% DMD/BMD patients have nonsense mutations in whom ataluren might be beneficial. The recommended dose is 40 mg/kg/day, divided in 3 doses (10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening) within 30 min of a meal. The most common side effect is vomiting. The clinical efficacy of Ataluren is not conclusively proven [Table 2]. Ataluren is approved by European Medical Agency but not by U.S. Food and Drug Administration (FDA). Two ongoing studies plan to confirm the benefit of ataluren in those patients with baseline 6MWDs between 300 and 400 m and to assess dystrophin expression in biopsy samples of ataluren-treated patients.

**Exon skipping**
Exon skipping is an RNA based approach using Antisense Oligonucleotide (ASO) to rebuild the reading frame by excluding specific exons from pre-mRNA transcript of dystrophin. In some patients, reading frame can be restored by skipping an extra exon adjacent to the deletion. The resulting transcript will be shortened but stable functional protein. Around 13%–14% of DMD patients have deletions potentially amenable to correction of reading frame by skipping exon 51 (e.g., exons 45–50, 47–50, 48–50, 49–50, 50, 52, and 52–63). Eteplirsen is an ASO which binds to exon 51 of dystrophin pre-mRNA and leads to exclusion of exon 51 during mRNA processing. It is the first exon-skipping drug to be approved by FDA (September 2016). This does not offer a cure, and it aims to lessen the muscular wasting process.

Another ASO, Golodirsen, is useful in patients with mutations amenable to exon 53 skipping (9% of DMD). FDA has rejected accelerated approval for Golodirsen. Two major concerns raised by FDA on Golodirsen are risk of infections and renal toxicity. Both these drugs are delivered as weekly intravenous infusions. Recommended dose of Eteplirsen is 30 mg/kg weekly intravenous infusion.

| Table 1: Therapeutic strategies in Duchenne muscular dystrophy |
|---------------------------------------------------------------|
| **Mechanism** | **Drug** | **Specific action** |
| Rectifying the primary defect (lack of dystrophin protein) | Nonsense suppression | Ataluren | Exon 51 skipping |
| | Exon skipping | Eteplirsen | Exon 53 skipping |
| | | Golodirsen | Exon 45 skipping |
| | | Casimersen | GALGT2 gene therapy to modulate utrophin expression |
| Utrophin modulation | rAAVrh74.MCK.GALGT2 | |
| Gene therapy | rAAVrh74.MHCK7.Micro-dystrophin | Microdystrophin gene therapy - AAVrh74 vector |
| | SGT-001 | Microdystrophin gene therapy, AAV9 vector |
| | PF-06939926 | Minidystrophin gene therapy, AAV9 vector |
| Targeting the downstream pathophysiological mechanisms | Anti-inflammatory | Corticosteroids (deflazacort and prednisolone) | |
| | | Vamorolone | |
| | | Edasalonexent | |
| | | Domagrozumab | |
| | | Taldipercept alfa | |
| | | Idebenone | |
| | | Pamrevlumab | |
| Myostatin inhibition (muscle regeneration) | NF-κB inhibitor | |
| Others | HDAC inhibitor | |
| | Humanized monoclonal antibody against myostatin | |
| | Human IgG1(Fc)‑adnectin fusion that binds myostatin | |
| | Modulating mitochondrial function and metabolism | |
| | Anti-fibrosis: Human monoclonal antibody against | |

CTGF: Connective tissue growth factor, HDAC: Histone deacetylase inhibitors, NF-κB: Nuclear factor kappa B, AAV: Adenovirus vectors

| Table 2: Clinical trials on Ataluren |
|------------------------------------|
| **Study** | **n** | **Study design and Intervention** | **Result** |
| Finkel et al.[7] | 26 | Phase 2 trial | Mean decline in 6MWT was lesser for low dose ataluren compared to placebo. No difference between high dose ataluren and placebo |
| Bushby et al.[8] | 174 | 48 weeks: High dose (80 mg/kg), low dose (40 mg/kg) and placebo arm | No significant difference in change in 6MWT (primary outcome). Post-hoc subgroup analysis showed some benefit |
| ACT-DMD trial[9] | 228 | 48 weeks: 40 mg/kg/day versus placebo | |

6MWT: 6-min walk test, ACT-DMD: Ataluren in patients with nonsense mutation Duchenne muscular dystrophy
over 1 h. Casimersen is exon 45 skipping drug (8.1%–9% of all DMD are amenable to exon 45 skipping).

The clinical efficacy of Eteplirsen and Golodirsen are not conclusively proven. A clinically meaningful change in dystrophin levels is not yet known in humans.

**Surrogate outcome (dystrophin production)**
Both the drugs have been shown to produce small increase in dystrophin. An open-label phase 2 dose-escalation study using Eteplirsen on 19 DMD patients with amenable deletions to exon 51 skipping showed dose-related increase in dystrophin production.[10] Mendell et al. had assessed the efficacy of Eteplirsen (30 mg/kg/dose and 50 mg/kg/dose) using a placebo-controlled randomized controlled trial (RCT) (1:1:1) for 24 weeks with dystrophin production (muscle biopsy) as the primary outcome. In the 30 mg/kg/dose arm, after 24 weeks, there was a greater change from baseline in percentage of dystrophin fibers compared to placebo (23% vs. −4%; mean difference = 27%), even though the actual dystrophin levels were very low.[11] Muscle biopsy was not done for 50 mg/kg/dose arm at 24 weeks. The trial had a further 24 weeks of open-label extension where everyone received Eteplirsen where at 48 weeks, the increase in dystrophin-positive fibers for the Eteplirsen 30 mg/kg was 52% and 50 mg/kg groups was 43%. In an open-label extension study for 36 months with comparison using historical controls, the average level of dystrophin in Eteplirsen-treated patients was 0.93% of that in healthy subjects. Golodirsen was studied in SKIP-NMD trial (phase 1/2 RCT of DMD patients amenable to exon 53 skipping) where once-weekly intravenous infusions of 4, 10, 20, and 30 mg/kg of Golodirsen or placebo were used for 12 weeks.[12] It was continued with open-label extension of all patients for 168 weeks and an additional 13 patients who were receiving weekly 30 mg/kg/dose of Golodirsen. At 48 weeks, the mean dystrophin levels had increased to 1.019% of normal (standard deviation 1.013) with absolute increase of 0.918% (P < 0.001).

**Six-minute walk test**
Mendell et al. showed that Eteplirsen-treated patients displayed a slower rate of decline in ambulation measured by 6-min walk test (6MWT) (mean change in 6MWT distance of 0.3 M for 50 mg/kg/dose, 128 M for 30 mg/kg/dose, and 26 M for placebo). When two patients in 30 mg/kg/dose arm were removed from analysis as they showed rapid disease progression soon after recruitment, this arm showed an increase of 14 M in 6MWT compared to baseline. There was no significant difference between the treatment arms. When compared with age and genotype matched 13 historical controls taken from DMD natural history registries, Eteplirsen-treated patients showed a statistically significant difference in lesser decline of 6MWT (148 M, P = 0.0052) by 3rd year and 4th year (162 M, P = 0.0005). Only two patients (17%) lost ambulation in Eteplirsen treated group compared to ten patients (77%) in control group, and even the rate of loss of ambulation was better in Eteplirsen-treated group (17% vs. 85%; P = 0.011).

**Pulmonary function**
The annual rate of decline of forced vital capacity (FVC) in open-label trial conducted on ambulatory DMD patients over 4 years was 2.19% annually and in a trial conducted on nonambulatory DMD patients over 2 years it was 3.66%. This is low compared to the natural history of around 5% annual decline in DMD patients irrespective of steroid treatment.[13] In an ongoing Phase 3, open-label study also showed an annual decline of 3.79% in FVC on interim analysis.[14] When compared with steroid-treated, age-, and genotype-matched DMD patients, Eteplirsen-treated group had a significant lesser decline in FVC.

**Adverse events**
No major adverse events were attributed to Eteplirsen. Common reported adverse events are procedural pain, contact dermatitis, vomiting, hypokalemia, and hematoma.

**Uncertainty and Equipoise**
The current evidence based on randomized data is limited by surrogate end points and very small sample size. Clinically meaningful threshold for dystrophin expression is not yet known. We still do not know the optimal timing for initiation of treatment, its long-term efficacy/adverse events. Use of historical controls can create bias since there is change in diagnostic ability, standard of care, and heterogeneity in disease. Moreover, the current functional outcome (6MWT) may not capture all functional capabilities and better outcome measures are needed. The current available data are promising and need to be confirmed in larger randomized controlled trials.

**Gene therapy**
Due to large size of dystrophin protein, gene replacement therapy is likely to be feasible only using large Adeno associated virus (AAV). Even then dystrophin coding exons cannot fit into AAV vectors. The current gene therapy strategy in DMD is use of smaller versions of dystrophin which can be packed in an AAV ("Microdystrophin" or "Minidystrophin"). There are three ongoing trials using Microdystrophin gene therapy with AAVs [Table 1]. Two alternative AAV-based gene therapies in dystrophinopathies
are surrogate gene transfer (GALGT2) and viral-mediated exon skipping.

**Surrogate gene transfer (GALGT2)**

GALGT2 naturally acts at synaptic regions, and its overexpression leads to ectopic expression of utrophin, a dystrophin homolog. Overexpression of utrophin in mice models prevents them from developing muscular dystrophy. Thus, overexpression of GALGT2 may improve DMD phenotype by increasing utrophin expression. GALGT2 has broad therapeutic potential in the muscular dystrophies.

**Viral-based exon skipping**

Alternative to using ASO for exon skipping, viral vectors can be used to deliver antisense sequence into the cells. Viral vectors like AAV can carry modified small nuclear RNA (snRNA) like U7 snRNA and they can induce exon skipping. When targeted to the appropriate exon, U7 snRNA therapy interferes with assembly of spliceosome and not translated into a protein. U7 Antisense design consists of optimized sequences targeting either splice acceptor or donor sites.

Major advantages of AAV delivery of U7 snRNA to induce DMD exon skipping over ASO induced exon skipping is that AAV vectors yield stable *in vivo* expression, and there is lesser need for frequent administration. It can effectively infect most muscles including cardiac muscle.[14]

**Limitations of gene therapy**

Since micro or minidystrophin protein is not the same as full dystrophin protein, even if gene therapy works perfectly in ideal scenario, it cannot cure DMD. There will still be disease progression even though at a slower rate. Microdystrophins are not the same as BMD isoforms. Patients who are seropositive to AAV vectors cannot be treated with this gene therapy. The durability of gene therapy is also ambiguous as AAV genome does not integrate with host genome with microdystrophin transgene remaining as an episome. They will be diluted in tissues with active cell division. Repeating the dose is difficult unless host immunity is suppressed or by using a different vector.

**Alternate translational initiation: Therapeutic utilization of a dystrophic exon 5 internal ribosomal entry site**

Premature termination codons in exon 1 and 2 (p.Trp3X, p.Glu5ValtsX3, and p.Gln17X) in DMD causes a very mild clinical phenotype. Exon 1 mutation (p.Trp3X) initiates translation at two AUG codons in exon 6, producing a protein lacking amino acid coded by exons 1–5. This downstream translation is propelled by exon 5 internal ribosomal entry site (IRES).[14,15] The most common single exon duplication seen in human DMD gene is duplication of exon 2 which leads to premature termination and severe phenotype as duplication prevents translation from the IRES in exon 5. However, deletion in exon 2 does not disrupt IRES translation. Hence, in patients with exon 2 duplication, exon 2 deletion can be created using exon skipping and thus activate IRES to produce functional near-normal dystrophin protein. Nearly 6% of patients with DMD carry exon duplication. Exon 2 duplication is typically associated with DMD and not BMD. Skipping of exon 2 has a very large therapeutic window. Viral delivered U7/snRNA-mediated skipping of exon 2 results in prolonged expression of dystrophin protein isoforms.

**TARGETING THE DOWNSTREAM PATHOPHYSIOLOGICAL MECHANISMS**

**Anti-inflammatory**

Corticosteroids have been the main drug therapy for DMD patients. Even though their exact mechanism of action is unknown, anti-inflammatory, immunomodulation, gene regulation, muscle fiber repair, and cell signaling alteration are the postulated mechanisms. Studies have shown them to increase muscle strength, extend ambulation, delay scoliosis/cardiomyopathy onset, decrease need for surgery, and preserve respiratory function.[16] Patients treated with long-term steroids have risk of adverse events. Prednisone, prednisolone, and deflazacort are the commonly used steroids. Current evidence comparing prednisolone and deflazacort is limited by few good-quality trials and selective reporting. Deflazacort might be having better motor outcomes, but uncertainty exists due to inconsistency in results among and within the trials. Among adverse events, weight gain is more with prednisolone while cataract and growth reduction are more with deflazacort. FDA approved deflazacort in 2017. Most ongoing interventional trials in DMD have steroid treatment as prerequisite for inclusion. FOR-DMD is an ongoing randomized double-blind trial comparing daily prednisone, intermittent prednisone (10 days on and 10 days off), and deflazacort.[17]

The major uncertainties regarding steroids are: (a) whether steroids should be started early in life, (b) whether steroids should be given in late-stage/wheelchair-dependent patients, (c) is there a stage where steroids are no longer of any benefit, (d) which regimen is superior? (e) effect of concomitant newer therapies, and (f) role of steroids in gene therapies.

Vamorolone is a novel first in class steroid analog. Glucocorticoids have two actions pertaining to NFkB:
SMA is an autosomal recessive condition which occurs most commonly (95%–98%) due to the homozygous deletion of both copies of exon 7 in survival motor neuron 1 (SMN1) gene on chromosome 5q which generates SMN protein required for development of motor neuron. Around 2%–5% is due to compound heterozygosity (SMN1 exon 7 deletion in allele 1/SMN1 intragenic mutation in allele 2). SMN 2 gene is similar to SMN 1 gene except for a silent mutation in exon 7 and it creates a predominantly unstable SMN protein in small quantity (10%–15%) of correctly spliced functional protein. All SMA patients lack a functional copy of SMN1 but retain a variable number of SMN2. Higher copy numbers of SMN2 correlate with milder disease and it is the most significant phenotypic modifier. Other genetic modifiers such as PLS3, NCALD, and CORO1C have been found to influence disease severity and symptoms.

Management strategies consists of maximizing motor function, enabling communication, providing better quality of life and access to new treatment. The first disease modifying treatment approved by FDA in 2016 was an ASO, Nusinersen (Spinraza). It binds to SMN2 pre-mRNA downstream of exon 7 causing translation of a fully functional SMN protein. The drug is administered intrathecally (12 mg; 5 ml) as it does not cross blood brain barrier; on day 0, 14, 28, and 63 and every 4 monthly maintenance doses [Table 3].

Nusinersen showed significant decrease (47%) in the risk of death or permanent assisted ventilation (HR [95% confidence interval [CI]: 0.53 [0.32, 0.89], P = 0.005) and lesser number of patients died or needed permanent ventilatory support (31/80; 39% vs. 28/41; 68%). The mean Hammersmith Infant Neurological Examination–Section 2 score improved over the course of treatment in Nusinersen arm whereas there was no improvement in the sham arm. Nusinersen arm had significantly more responders (≥4 point increase) in Children’s Hospital of Philadelphia Infant Test of Infantile onset SMA with two SMN copies. Nusinersen showed significant decrease (47%) in the risk of death or permanent assisted ventilation (HR [95% confidence interval [CI]: 0.53 [0.32, 0.89], P = 0.005) and lesser number of patients died or needed permanent ventilatory support (31/80; 39% vs. 28/41; 68%). The mean Hammersmith Infant Neurological Examination–Section 2 score improved over the course of treatment in Nusinersen arm whereas there was no improvement in the sham arm. Nusinersen arm had significantly more responders (≥4 point increase) in Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders score compared to sham arm (n1,%; Nusinersen, 52/71 Vs Sham, 1/3).

CHERISH trial assessed the efficacy of Nusinersen in children with SMA (Types II or III) aged 2–12 years. The trial was stopped early after prespecified interim analysis on primary outcome (Hammersmith Functional Motor Scale-Expanded; HFMSE) showed significant superiority of least square mean increase from baseline HFMSE score favoring Nusinersen compared to sham arm. The responder rates (≥3-point increase in

Spinal muscular atrophy
SMA is a genetic anterior horn cell disorder and is the most common genetic cause of infant and toddler death. There is progressive loss of motor neurons in the spinal cord and brain stem. Clinical features include gross motor delay, muscle atrophy, weakness, difficulty breathing/swallowing, poor weight gain, scoliosis, hip problem, and contractures. There are 4 subtypes of SMA (Type 0: Prenatal/fetal; Type 1: <6 months; Type II: 6–18 months; Type III: >18 months; Type IV: 20 yrs to 30 yrs). SMA is a neurodegenerative disease with all subtypes deteriorating with time. Early-onset SMA without treatment can worsen quickly with early death. However, all the subtypes except prenatal has an asymptomatic period where there is a narrow therapeutic window for intervention.

Idebenone was assessed in RCT (DELOS trial) of 64 steroids naïve, mostly nonambulant DMD patients. Idebenone significantly reduced the decline in respiratory function at 52 weeks, compared with placebo.[22] An ongoing trial is testing the efficacy of Idebenone in DMD patients taking steroids (SIDEROS trial).[23]

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HFMSE score) were more in Nusinersen arm (odds ratio, 95% CI; 6 [2–15]).

Interim analysis of ongoing single arm study (NUTURE of Nusinersen treatment in 25 presymptomatic infants with 2 or 3 copies of SMN2 showed that all children were alive (median age 26 months, median time on treatment 27.1 months) and none required permanent ventilatory support. Four children required respiratory intervention (all with 2 copies of SMN2). All children achieved sitting without support, 22/25 (88%) achieved walking with assistance, and 17/25 (68%) achieved walking independently.

Treatment related adverse events were rare in Nusinersen trials, and most of the reported adverse events were related to lumbar puncture. Risk of thrombocytopenia and renal toxicity are the two safety concerns highlighted in the prescribing information.

Limitations and concerns: Narrow inclusion criteria and smaller sample size affects generalizability of results. There is lack of long-term data on safety and efficacy. There is uncertainty on long-term effects of repeated lumbar puncture.

ONASEMN OGEBEPAVOREC (ZOLGENSMA, AVXS-101)

The new gene therapy, recently approved by FDA, utilizes adeno-associated virus serotype 9 vector to deliver a copy of SMN to supplement the defective SMN1. It is administered as one time intravenous administration. The evidence for efficacy comes from an open label two-cohort clinical trial on Type I SMA along with its extension study (START). Three patients received low dose (6.7 × 1013 vg/kg of body weight), and 12 received a high dose (2.0 × 1014 vg/kg). The primary outcome was safety while secondary outcome was the time until death or the need for permanent ventilatory assistance. All infants were alive after 24 months of follow-up compared to 8% survival in historical cohort. There was an increase of 9.8 points at 1 month and 15.4 points at 3 months with a mean change of 24.6 points from baseline. At the end of 24 months, 92% attained head control and 17% could walk unassisted. In the START follow-up study, two more achieved standing with support. There is no evidence for use of this drug in Type II/III SMA. Trials are ongoing in presymptomatic SMA patients. Major adverse events noted in the trial were elevated aminotransferases which subsided with steroids.

Major limitations are small sample size, lack of randomized controlled trials, use of historical controls, uncertainty over the duration of expression of this gene therapy, antibody formation against AAV vector, liver toxicity, lack of long-term follow-up data, and huge cost.

RISDIPLAM

Risdiplam is an orally administered small molecule which is distributed centrally and peripherally and modulates SMN2 pre-mRNA splicing to increase SMN protein levels. The three ongoing studies on SMA I, II, and III are SUNFISH, JEWELFISH, and FIREFISH. SUNFISH is a multicenter randomized double-blind study on SMA II or III, aged 2–25 years for 12 months. FIREFISH examines risdiplam in Type I SMA, 1–7 months old with two SMN2 copies. JEWELFISH trial tests risdiplam in any type of SMA with age between 6 months and 60 years and those who had participated in any SMN2 targeting therapies. The interim analysis of these trials is promising with no major serious adverse events reported.
CONCLUSIONS

The field of inherited neuromuscular disorders is going through an exciting period where bench to bedside translation is happening at a rapid phase. Newer innovative therapies like ASOs bring new hopes to the patients with these otherwise devastating diseases. Accessibility, affordability, and cost-effectiveness of these drugs are a major issue in developing countries like India. Access for patients to participate in clinical trials is also need of the hour. Realistic expectations on the efficacy of these drugs with meticulous collection of long-term safety and efficacy data will pave way to greater optimism regarding management of these inherited neuromuscular disorders.

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Conflicts of interest

There are no conflicts of interest.

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