Current Neurology and Neuroscience Reports (2020) 20: 14
https://doi.org/10.1007/s11910-020-01034-6

PEDIATRIC NEUROLOGY (W. E. KAUFMANN, SECTION EDITOR)

Update on Muscular Dystrophies with Focus on Novel Treatments and Biomarkers

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Published online: 14 May 2020
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Abstract

Purpose of Review Muscular dystrophies are a heterogeneous group of inherited muscular disorders characterized by progressive muscle weakness and in many cases cardiac and respiratory muscle involvement. Historically, these disorders are considered incurable with grave prognoses. The genes responsible for most muscular dystrophies are known, and early diagnosis is achievable with proper clinical recognition and advanced genetic testing. This article reviews recent advances in the development of novel treatments and biomarkers in the realm of muscular dystrophies commonly encountered in pediatric population.

Recent Findings The therapeutic landscape of muscular dystrophies has changed with the development of new approved treatments for Duchenne muscular dystrophy (DMD), the most common and severe muscular dystrophy. This has paved the way for the development of novel therapeutic strategies for not only DMD but also other muscular dystrophies.

Summary This article reviews recent advances in the development of novel treatments and biomarkers in the realm of muscular dystrophies commonly encountered in pediatric population.

Keywords Muscular dystrophy · Duchenne muscular dystrophy · Limb girdle muscular dystrophy · Myotonic dystrophy · Emery-Dreifuss muscular dystrophy · Congenital muscular dystrophy

Introduction

Muscular dystrophies are a heterogeneous group of inherited muscular disorders characterized by progressive muscle weakness. Historically, these disorders are considered to be difficult to treat. In the last three decades, there is a tremendous progress in molecular and genetic basis of these disorders; early diagnosis is achievable with proper clinical recognition and advanced genetic testing. Here, we review recent advances in the development of novel treatments and biomarkers for muscular dystrophies commonly encountered in pediatric populations.

This article is part of the Topical Collection on *Pediatric Neurology*

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Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a severe, degenerative, X-linked recessive muscle disease with an incidence of 1:3500–5000 males [1–3]. The dystrophin gene (*DMD*), with 79 exons, is one of the largest known human genes and produces dystrophin, a structural protein located on the cytoplasmic face of skeletal and cardiac muscle membranes. Two-thirds of mutations are large deletions of one or more exons; the rest are due to insertions, small deletions, point mutations, or splicing mutations [4–6]. DMD is caused by out-of-frame mutations leading to complete loss of dystrophin protein, whereas Becker muscular dystrophy (BMD) is caused by in-frame mutations resulting in milder phenotypes due to a truncated protein [7,8]. Although there is phenotypic variability, DMD patients typically present between 2 and 5 years of age with delayed motor milestones, falls, toe-walking, calf hypertrophy, very high creatine kinase (CK) levels, and typically mild cognitive impairment [1,2]. Progressive muscular damage and degeneration eventually leads to loss of ambulation, respiratory impairment, and cardiomyopathy. Genetic testing is confirmatory of diagnosis.

Review of DMD Therapeutic Strategies

There are multiple therapeutic strategies in the development for DMD; the majority are targeted at respiratory and muscular functions and do not directly address the cognitive components of the disease.

Anti-Inflammatory Therapies

Current practice parameters recommend oral corticosteroids (prednisone or deflazacort) in all DMD patients in the early ambulatory phase [1,2]. Corticosteroids have been shown to prolong ambulation, reduce decline in cardiopulmonary function and risk of scoliosis, and improve life expectancy [9,10]. However, corticosteroids have significant side effects, including weight gain; deflazacort, though, has been associated with less weight gain compared with prednisone [11]. A post hoc analysis of the placebo arm from the Ataluren study for DMD showed improved outcomes in deflazacort-treated patients as well [12•]. A 5-year, randomized, double-blind study comparing daily deflazacort, daily prednisone, and intermittent (10 days on, 10 days off) prednisone has been completed; results are pending [13].

Dystrophin-deficient myofibers are vulnerable to mast cell granule-induced necrosis; thus, CRD007, a mast cell inhibitor, is in early investigation as a non-steroidal agent to decrease inflammation [14, 15]. Ilaris/Canakinumab, targeting the inflammatory cytokine IL-1β, is also in early-phase studies.

Agents Targeting Signaling Pathways

Another therapeutic angle in DMD is reduction of inflammation and fibrosis. A key driver in DMD is muscle fiber degeneration from inflammation due to chronic NF-κB activation [16]. Newer agents selectively targeting NF-κB pathways lack the systemic toxicity of oral corticosteroids [2]. Vamorolone is a steroid analog with membrane-stabilizing and anti-inflammatory properties (including inhibition of NF-κB) [17]. A double-blind, placebo- and prednisone-controlled clinical trial is currently enrolling DMD patients [18]. Edasalonexent is an inhibitor of NF-κB [19]. A phase 2 trial in DMD patients had shown promise [20], and the agent is currently undergoing a phase 3 study in steroid-naïve DMD patients.

Antioxidants

Reactive oxygen species (ROS) render muscle cells susceptible to injury via increased membrane permeability, protein degradation, activation of the inflammatory cascade, and mitochondrial dysfunction; ROS reduction may help improve muscular function.

Idebenone, a synthetic short-chain benzoquinone and coenzyme Q10 derivative, plays an important role in restoring mitochondrial function through its role in mitochondrial electron transport chain [21]. A phase 3 study in DMD patients not using corticosteroids demonstrated improved pulmonary function [22]. A phase 3 study of idebenone for DMD patients (SIDEROS) on oral corticosteroids is currently underway [23].

(+)-Epicatechin, a cacao flavonoid, has previously demonstrated benefits in mitochondrial function, oxidative stress, and muscle function in a mouse model of limb girdle muscular dystrophy (LGMD) and is being investigated for DMD [24]. Epigallocatechin gallate, a major polyphenol found in green tea, has shown in vivo reduction in serum CK, reduced time to maximal force, and increased utrophin significantly in mouse model [25].

Anti-Fibrotic Agents

Agents aimed at downregulating transforming growth factor-β (TGF-β) have been shown to decrease fibrosis in some preclinical DMD models [26–28]. Losartan, a antihypertensive agent with similar function, has been studied in DMD patients but failed to show significant functional benefit [29,30].

Connective tissue growth factor (CTGF) promotes fibrosis and reduces muscle fiber regeneration. Pamrevlumab (GF-3019) is a humanized monoclonal antibody against CTGF which is undergoing a phase 2, open-label study in non-ambulatory DMD patients [31].

Histone deacetylase (HDAC) inhibitors have been shown to activate gene expression and to have beneficial role in the mdx mouse model [32]. Givinostat is an HDAC inhibitor that has anti-inflammatory, anti-fibrotic, and regenerative properties, which is in a phase 3 study in ambulatory DMD patients [33].

Phosphodiesterase 5A Inhibition

One effect of defective dystrophin includes reduced or lack of functional nitric oxide (NO)-generating enzymes (due to lack of dystrophin anchoring), affecting muscle perfusion [34]. It was postulated that phosphodiesterase (PDE) inhibition (PDEi) would increase muscular perfusion, thereby reducing muscular degeneration. Sildenafil (short-acting PDEi) and tadalafil (long-acting PDEi) demonstrated some evidence of reduced muscle damage with exercise in DMD animal models. However, a phase 3 study in DMD patients found no significant effect of tadalafil on a 6-min walk distance (6MWD) [35].

Muscle Structure Stabilization and Optimization

Myostatin Inhibition

Myostatin (growth differentiation factor 8, GDF8) regulates muscle growth and limits skeletal muscle growth to prohibit

abnormal hypertrophy by inhibition of myoblast maturation; thus, inhibition results in increased muscle mass and reduction of fibrosis [36]. Some compounds have already been investigated, and development ceased due to lack of clear improvement [37–41]. ACE-031 is another myostatin inhibitor and is a fusion protein of activin receptor type IIB and IgG1-Fc, which binds myostatin and related ligands. Although a trend of maintained 6MWD versus the decline in placebo groups was noted, early-phase trials were stopped due to epistaxis and telangiectasias [42]. Despite these setbacks, further development is expected.

Utrophin Modulation

Utrophin, present during both fetal development and muscle regeneration, has significant homology to dystrophin but is expressed mostly at neuromuscular junctions [43,44]. Dystrophin-utrophin double mutants showed more severe muscle weakness than dystrophin-only mutant mice [45–47]. Ezutromid was identified as a promising agent to increase utrophin expression in DMD; however, a phase 2 study in ambulatory DMD patients failed to demonstrate efficacy, and the study was terminated [48,49].

Another strategy of utrophin expression modulation is being investigated through adeno-associated virus (AAV)-mediated gene delivery of the GALGT2 gene to effect GALGT2 overexpression [50]. GALGT2 normally acts at the synaptic regions to add the terminal GalNAc to an O-linked carbohydrate antigen on the α-dystroglycan near the neuromuscular junctions [51]. Overexpression of GALGT2 results in ectopic expression of many synapse-associated proteins, including utrophin, away from the synaptic regions [51], thereby ameliorating DMD phenotype. A study of AAVrh74-mediated GALGT2 gene delivery is currently recruiting patients [50].

Improvement of Cardiac and Respiratory Function

CAP-1002 is a novel therapeutic approach where allogenic cardiocyte precursor stem cells are administered directly to the heart via cardiac catheterization of coronary arteries to treat cardiomyopathy in DMD patients; currently, it is in phase 1/2 studies and some scar size reduction and inferior wall improvements have been seen [52]. Rimeporide, a sodium-proton exchanger (NHE-1) inhibitor, initially developed for heart failure, has been granted orphan drug status in Europe for a similar indication in DMD.

Carmeseal-MD/P-188 NF targets muscle membrane stabilization by its amphiphilic structure properties, in order to improve cardiac, respiratory, and muscular weakness based on preclinical studies that demonstrated reduction in respiratory function decline [53].

Dystrophin Protein Function Restoration

A major target of DMD therapy mechanism has been the restoration of function of the defective dystrophin; multiple techniques have been developed to attain this.

Exon Skipping

In exon skipping, a functional protein product is salvaged by the use of synthetic antisense oligonucleotide (ASO) targeted at the messenger RNA level to skip out-of-frame mutations resulting in reading frame restoration [2]. Exon skipping strategies are amenable to about 80% of all DMD mutations; of these, 13% are amenable to exon 51 skipping [54].

The first ASO clinical trials involved exon 51 skipping using the compounds drisapersen [55] and eteplirsen [56•]. Drisapersen did not receive FDA approval, and subsequent development was stopped. Eteplirsen received accelerated FDA approval in 2016 based primarily on a small trial (n = 12) that demonstrated a 23% increase in dystrophin-positive muscle fibers and 6MWD improvement [8], which made it the first drug to receive FDA approval using dystrophin quantification as a surrogate outcome measure for DMD. Additional ASOs are currently in phase 3 studies for ambulatory DMD patients: casimersen (exon 45) and golodirsen (exon 53) [57]. Others are in phase 1/2 trials: PRO044 (exon 44) and suvodirsen (exon 51) [58–60]. About 9% and 10% of DMD patients may be amenable to casimersen and golodirsen, respectively. Of note, 2% of patients on golodirsen are amenable to eteplirsen, as deletion of exon 52 is amenable to either exon 51 or 53 skipping [61].

Preclinical data on peptide-conjugated phosphorodiamidate morpholino oligomers (PPMO), which are ASOs with neutral DNA analogs, have shown promise with improved muscle cell penetration, favorable pharmacokinetics, and notable penetration into the heart and diaphragm [62,63]. SRP-5051, a PPMO for exon 51 skipping, is currently being studied in a phase 1 study [64]. Three other exon-skipping programs are also underway: NS-065 for exon 53 skipping [65], WVE-210201 for exon 51 skipping [66], and DS-5141b for exon 45 skipping [67].

Nonsense Suppression

Nonsense mutations account for about 10–15% of DMD patients; they generate a stop codon, resulting in truncated and nonfunctional proteins [61,68]. The read-through strategy results in suppression of the stop codon, leading to the production of partially functional dystrophin [69]. Proof of efficacy was initially demonstrated by the aminoglycoside antibiotic gentamicin [70]. Ataluren, an oral medication with a better safety profile, promotes read-through of the premature stop codon [71]. A phase 2 trial revealed increased dystrophin

expression on muscle biopsy, which led to conditional approval in Europe [72]. A phase 3 study did not show improvement in 6MWD in all DMD patients and was not approved by the FDA [73]. Further studies in ambulatory DMD patients are underway to address these concerns, as well as other compounds, such as arbekacin sulfate.

Gene Therapy

Restoration of the normal dystrophin gene would be ideal; however, the dystrophin gene's size makes packaging inside viral vectors difficult. Interestingly, a BMD patient was found to be ambulatory at age 61 with deletion of exons 17–48 [74]. This resulted in the development of micro- and mini-dystrophin constructs small enough to be packaged in AAV and ultimately inserted into host genome [75]. These translate into functional products to modify DMD phenotype severity. Three gene therapy programs are using this principle in phase 1 trials using different AAV vector serotypes and different promoters to augment expression of dystrophin in the muscle cells through one-time intravenous infusions. These are AAVrh74 capsid with an MHCK7 promoter [76,77], AAV9 capsid with a CK8 promoter [78,79], and AAV9 capsid with an unspecified muscle-specific promoter [80,81]. Although this appears to be a promising approach independent of DMD gene mutation, there are concerns regarding the duration of the response, need for re-dosing, and rare possibilities of integration in host genome of the viral vector with associated immune responses [82,83]. In addition, AAV insertion of follistatin, an antagonist to myostatin (i.e., myostatin inhibition), is being investigated.

CRISPR/Cas9

Another approach is offered by the discovery of the clustered regularly interspaced short palindromic repeats (CRISPR) technology, in which an endonuclease called Cas9 can cleave the genome in a precise manner when coupled with a strand of guide RNA [84,85]. In vitro studies have shown that the CRISPR/Cas9 technology can be employed for a number of different mutations including patients with exon or multi-exon deletions [86,87]. This technology can allow gene editing to be implemented in virtually all DMD mutations, providing tremendous potential for individualized treatment [84].

As these therapies develop, it will be critical to evaluate combination regimens that work synergistically to improve the clinical symptoms and overall quality of life of DMD patients.

Biomarkers

Although there has been tremendous progress in therapy development, fewer efforts have been dedicated to reliable DMD biomarker development. The most commonly used disease progression measures used in clinical trials include various functional scales such as the most commonly used 6MWD as well as the motor function measure (MFM) and North Star Ambulatory assessment (NSTAR) rating scales [88]. However, these measures are subject to individual variation and patient motivation.

The most widely known, currently used diagnostic biomarker is serum CK. Although useful for basic screening in appropriate clinical settings, it is a weak pharmacodynamic biomarker and surrogate endpoint for DMD [89,90]. Measurement of CK in a dried spot test can be used in newborn screening for early detection of DMD and other muscular dystrophies [88].

While dystrophin analysis via immunohistochemical staining (IHC) or western blot (WB) in muscle biopsy specimens had been used for DMD diagnosis in the past, they are rarely performed today. However, with the advent of gene-based therapies to restore dystrophin protein, dystrophin analysis via IHC and WB has been used as monitoring biomarkers as surrogate endpoints for efficacy. Despite this, clinical correlation between functional outcome measures and expression of dystrophin protein in biopsies has been weak.

Magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) are useful noninvasive techniques that assess muscle tissue and thus, disease progression [91–94]. MRI offers reliable reproducible quantification measures across centers involved in clinical trials and does not depend on patient motivation. However, discomfort associated with immobilization and costs can be prohibitive outside of the clinical trials [94].

There are several prognostic biomarkers to help predict disease severity. Latent TGFβ binding protein 4 (LTBP4) has been identified as a genetic modifier that correlates with age of ambulation loss [95,96]. Various potential metabolic/inflammatory markers (CCL22, FCER2, insulin and leptin, metalloproteinases (MMPs), various fatty acids, and protein intermediaries) in blood or urine can be used as predictive and safety biomarkers, but none are confirmed to be useful for widespread clinical scale [88].

In addition, miRNAs or miRs have an intrinsic ability to function as gene silencers and modulate the synthesis of specific proteins [88]. miRNAs can be ideal biomarkers, as they are specifically expressed in different tissues and are released into the circulation upon injuries [97]. Some miRNAs have been found to be associated with clinical parameters indicative of disease progression in DMD, such as high miR-30c in patients with better preserved motor function and miR181 with worse outcome, but none were statistically significant [98].

Limb Girdle Muscular Dystrophy

LGMDs are a varied group of muscular dystrophies characterized by limb girdle weakness, elevated CK, and dystrophic

muscle biopsy [99]. In the pediatric age group, the common LGMDs are due to sarcoglycanopathies (clinically similar to DMD; due to mutations of 4 genes in the sarcoglycan complex), dystroglycanopathies, and calpainopathy [100]. There is no standard of care medical therapy for LGMDs and no specific biomarkers for diagnosis other than genetic testing.

Review of LGMD Therapeutic Strategies

Anti-Inflammatory

Corticosteroids are not standard of care, but earlier non-systematic studies have shown some positive response in sarcoglycanopathies and dystroglycanopathies [101,102]. On the other hand, there are reports of deleterious effects on cardiac tissue in animal models [103]. Recent mouse models have demonstrated intermittent prednisone dosing aids in muscle repair and reduce risk of atrophy or muscle adipogenesis [104]. A double-blind, randomized, placebo-controlled trial to determine the safety and efficacy of deflazacort in LGMD2I is actively recruiting [105]. However, a 2013 crossover study looking at deflazacort in LGMD2B patients found worsening of strength while on deflazacort, which improved upon drug discontinuation [106].

Anti-Oxidant

Similar to DMD, anti-oxidant therapies are being investigated, such as the aforementioned (+)-epicatechin cacao flavonoid and the epigallocatechin gallate green tea polyphenol [24, 25].

Anti-Fibrotic Agents

Modification of aberrant TGF-β signaling via angiotensin converting enzyme (ACE) inhibitors can reduce fibrosis similar to DMD [84]. CoQ10 and lisinopril (together and separately) are being investigated for reduction of cardiomyopathy in LGMD 2C-2F and 2I [107].

Anti-Myostatin

There is a phase 1/2 study of a humanized anti-myostatin in ambulant patients with LGMD2I, though it is not actively recruiting.

Gene-Based Therapies

Gene Replacement

Similar to DMD, AAV vector-based gene therapies are in the early stages of development: rAAVrh74.MHCK7 for LGMD2B, AAV1-gamma-sarcoglycan vector for LGMD2C, scAAVrh74.tMCK for LGMD2D, and scAAVrh74.MHCK7 for LGMD2E [108–112].

Antisense Oligonucleotide

In animal models, exon skipping of exons 4 and 7 of the gamma sarcoglycan may produce a functional truncated protein [113].

Myotonic Dystrophy

Myotonic dystrophy consists of two disorders: a trinucleotide (type 1, MD1, DMPK gene) and tetranucleotide repeat disorder (type 2, MD2, CNBP gene; does not manifest in children). MD1 can present as congenital, childhood, adult, or late-onset type [114]. Congenital myotonic dystrophy is the most severe phenotype with > 1000 CTG repeats. There is currently no approved medical treatment for myotonic dystrophy apart from symptomatic management of myotonia with mexiletine (classically) or other agents [115].

Gene-Based Therapies

RNA Modulation

AMO-02/tideglusib, a GSK-3β enzyme inhibitor, is being investigated for congenital MD [116]. The mechanism is to reduce the transformation of CUGBP1 (a protein that binds the defective mRNA generated by MD1 DMPK mutations) to a repressing form, which not only aggregates by itself in a toxic manner but also represses further RNA processing through subsequent complexing. Currently, a phase 1/2 trial assessing safety and efficacy is planned. DMPK SiRNA (e.g., NT0200) is being developed in an effort to interfere with the defective RNA product but currently is in the early stages of development [117].

Exon Skipping via ASO

AT466, an AAV ASO for exon skipping therapy, is currently in development stages. IONIS-DMPKRx, an ASO aimed to facilitate RNase H1-mediated degradation of DMPK RNA and reduce toxic RNA buildup, had development halted due to insufficient muscle concentration levels [118].

Biomarkers

Measuring alternatively spliced RNA products, before and after treatment, may be important future biomarkers of therapy response, as many therapies are targeted at RNA manipulation.

Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy (EDMD) is an uncommon heterogeneous disorder, involving different genes: EMD (Emerin), FHL1 (four-and-a-half LIM domains protein 1), LMNA (Lamin A/Lamin C), SYNE1/SYNE2, and TMEM43 (LUMA) [119]. Depending on the mutation, EDMD can result in X-linked recessive (EMD, FHL1), autosomal dominant (typically LMNA), or autosomal recessive inheritance. The hallmark findings in EDMD are early development of contractures, delayed motor development and progressive humeroperoneal weakness, and prominent cardiac abnormalities such as cardiomyopathy and cardiac conduction defects [119]. There are no specific biomarkers and no proven medical therapy for EDMD patients. Most studies are directed towards LMNA variant EDMD patients [84].

Anti-Inflammatory

An open-label observational study is investigating the role of oral corticosteroids in LMNA patients, as there is a high degree of inflammation seen in muscle biopsies [120].

Cardioprotective

ACE inhibition alone or in combination with MEK1/2 inhibition has been shown to improve left ventricular function in LMNA knockout mice [121]. Similarly activation of autophagy can improve cardiomyopathy [122], and inhibition of mTOR signaling pathway via rapamycin improves skeletal and cardiac myopathy in LMNA knockout mice [123]. None of these strategies have been tested in human subjects.

Defibrillators

It has been shown in a prospective trial that early use of implantable cardioverter-defibrillators can reduce arrhythmias and prevent sudden cardiac deaths in LMNA patients [124].

Gene-Based Therapies

All studies have been conducted only in animal models.

Exon Skipping

Skipping of exon 3 or 5 of LMNA gene can produce a functional truncated protein [125].

Gene Replacement

AAV-based gene replacement of Emerin has been proposed [84].

Gene Silencing

Allele-specific silencing of dominant LMNA mutations can be an effective treatment strategy [84].

Congenital Muscular Dystrophy

Congenital muscular dystrophies (CMDs) are a group of rare, heterogeneous muscle disorders that typically manifest at birth or within the first 2 years of life with hypotonia, delayed motor development, progressive muscle weakness along with elevated CK, and dystrophic muscle biopsy [126]. Although there are many subtypes, the three major subtypes are LAMA2 related (merosin-deficient CMD or MDC1A), collagen VI deficient (or Ullrich CMD and Bethlem myopathy), and dystroglycanopathies (due to mutations in dystroglycan or the numerous gene products that glycosylate it) [84].

There are no specific biomarkers; however, muscle imaging studies (ultrasound and MRI) are useful in differentiating CMD subtypes. Currently, there are no disease-specific therapies [126].

Anti-Apoptotic

In preclinical studies, it has been shown that omigapil prevents apoptosis and loss of muscle tissue [127]. A phase 1 study is evaluating the pharmacokinetic profile, safety, and tolerability of oral omigapil in pediatric and adolescent CMD patients (Ullrich CMD or MDC1A) [128].

Cyclosporin A has anti-apoptotic as well pro-autophagic properties. It is found to be effective in Ullrich congenital muscular dystrophy (UCMD) mouse and zebrafish models [129] and has been shown to reduce apoptosis in a pilot trial in patients with UCMD [130].

An open-label phase 2 trial of low-protein diet (which promotes autophagy and improved outcomes in mouse model of UCMD) [131] in patients with UCMD was recently completed; the results are not yet published [132].

Anti-Fibrotic

Losartan's blocking of TGF-β pathway has been shown to reduce fibrosis and improve disease phenotype in MDC1A mouse model [133].

Membrane Stabilization

The loss of muscle-matrix interaction plays a central role in the pathogenesis of MDC1A [84]. Intramuscular administration of laminin 111 (a homolog of laminin 211) has been shown to reduce apoptosis, increase fiber size, and improve muscle strength by stabilizing the interaction between the

muscle membrane and extracellular matrix (ECM) in LAMA2-deficient mice [134].

Agrin is an extracellular matrix protein that can serve as a bridge between the ECM and muscle membrane receptors, and mini-agrin has been shown to ameliorate phenotype in animal models [135].

Gene-Based Therapies

These are in preclinical stages of development.

Allele-Specific Silencing

ASO-based therapies have been shown to restore normal collagen VI fibers in patient-derived cell lines with dominant mutations associated with UCMD [136,137].

Exon Skipping

ASO-based exon skipping by removing a stop codon promotes merosin re-expression and mild improvement in a mouse model of MDC1A [138]. This approach has also been shown to be effective in animal models of Fukuyama CMD [139].

Gene Replacement

AAV-based gene replacement therapy is not feasible for MDC1A or UCMD because of the large gene size. Animal studies have shown some success in some of the dystroglycanopathy subtypes [140].

Overexpression of the glycosyltransferase LARGE mutations (rare cause of CMD) has shown promise by restoring glycosylation and improving pathology in different mouse models due to LARGE, FKRP, and POMGNT1 mutations [141]. However, it has also been shown that LARGE overexpression can aggravate the dystrophic phenotype, specifically in mouse models of MDC1A-, FCMD-, and FKRP-related CMD [142].

CRISPR/Cas9

CRISPR/Cas9 has been employed as a therapeutic strategy in MDC1A with a specific emphasis on splice site mutations (which account for up to 40% of mutations in MDC1A) [143]. This strategy led to successful correction of splice site mutation to result in inclusion of exon 2 in the LAMA2 transcript, resulting in restoration of full-length LAMA2 protein and significant improvement in muscle histopathology and muscle function in a new study of a MDC1A mouse model [144].

Conclusion

Muscular dystrophies are progressive inherited genetic disorders, historically considered untreatable. Due to the heterogeneity of the genetics of various muscular dystrophies, there is no panacea. Another challenging aspect is the development of robust biomarkers and clinical outcome measures from the natural history cohorts of these rare disorders to make them ready for clinical trials.

However, with improvement of general care, cardiac, and respiratory management, many severely affected patients are surviving well into adulthood.

Tremendous progress has been made in the last two decades in understanding the genetic and molecular basis of these disorders, resulting in the development of animal models and preclinical studies. This is paving the way for development of translational studies with a bench-to-bedside approach. Two drugs used for restoring dystrophin gene in a subset of DMD patients have been approved recently (one in USA, another in Europe), and several others are in the final stages of clinical development. The recent advent of gene-based therapies has opened a new door in therapeutic development as well. This has changed the treatment landscape for these once incurable genetic disorders and raises hope for meaningful therapeutic interventions.

Compliance with Ethical Standards

Conflict of Interest Dr. Neil Datta: reports no disclosures.

Dr. Partha S Ghosh: received consulting fees from CVS Caremark, Catalyst Pharmaceuticals, and ad hoc scientific advisory board member of Sarepta.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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