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Editorial

Therapeutic Advances and Novel Drug Treatment Opportunities in the Neuromuscular Disorders Area

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Abstract: Several molecular advances have transformed the treatment landscape in the field of neuromuscular disorders, bringing more genetic testing for screening, better biomarkers, new innovative therapies that target specific disease pathways and mechanisms, and a multidisciplinary approach to care. The field includes both genetic and acquired diseases, so the landscape is at various opportunity stages. These advancements have led to more precise diagnoses and personalized medicine in the management of neuromuscular disorders, which can be life-altering for patients. This Editorial examines how the emergence of new therapies impacts the survival and motility of children and adults with spinal muscular atrophy and Duchenne or Becker muscular dystrophy, limb girdle muscular dystrophy, late-onset glycogenosis type 2, myotonic dystrophy and facioscapulohumeral dystrophy. Advances over the past two decades have been substantial in myasthenia gravis (MG) the most common acquired neuromuscular transmission disorder. Despite the existence of few refractory cases, the goal of treatment is the complete remission of symptoms, achieved by thymectomy, immunosuppression, intravenous immunoglobulin, or monoclonal antibody. Advances have been substantial both for serum-positive and serum-negative MG patients who are benefitting from an expansion of treatments since more therapies are available. Also, in the field of metabolic disorders, the use of diet supplements and exercise appears important.

Keywords: deflazacort; vamorolone; acid alpha-glucosidase deficiency; enzyme replacement therapy; myotonic dystrophy type 1; facioscapulohumeral dystrophy; myasthenia gravis; eculizumab

1. Introduction

Neuromuscular diseases cover a wide range of acquired and inherited diseases, metabolic myopathies, mitochondrial and neuromuscular junction disorders. For most of them, treatment opportunities were, until recently, extremely poor or even non-existent, and often recommendations have been limited to conservative measures, physical activity, and lifestyle modifications.

In recent years, the development and application of new effective diagnostic tools, such as modern imaging techniques, histopathological studies, advanced genetic tools, and a better in-depth understanding of their underlying pathophysiology have led to an earlier diagnosis and improved therapeutic opportunities [1].

Recent developments in novel therapies for neuromuscular diseases offer new perspectives on patient management. Substantial progress is evident from the numerous clinical trials in the field and numerous drug and gene therapy opportunities.

In adult-onset Glycogenosis type 2 (GSD2) NeoGAA availability appears a step forward in improving Enzyme Replacement Therapy (ERT), this new enzyme preparation with better delivery to key muscles has demonstrated benefits in both trials and their extensions. NeoGAA is available and most patients might accept the switch from al-glucosidase alpha in ERT, as observed in the extension phase, its use might change the dosage, targeting tissue delivery.

Both Myotonic dystrophy and facioscapulohumeral dystrophy, two common neuromuscular disorders reveal possible ways to slow down their progressive muscle atrophy course.

Myasthenia Gravis (MG) is the most common neuromuscular transmission disorder [2]. Despite the existence of few refractory cases, the goal of treatment is the complete remission of symptoms and the selection of the therapeutic strategy should rely on phenotypical characteristics, serological subtypes, and comorbidities.

2. Spinal Muscular Atrophies (SMA)

Major advances have changed the treatment and perspective for both neonatal SMA and adult patients, posing the question of the utility of neonatal screening. Novel drugs are increasingly used to target specific molecules involved in these disorders. For example, nusinersen [3] and risdiplam have been developed to target RNA splicing defects in SMA [4]. Previous research in these inherited muscular disorders suggests that therapies directly targeting gene mutations are possible [5–7]. Currently, there are three approved treatments for spinal muscular atrophy. These are Nusinersen (Spinraza), an antisense oligonucleotide, Onasemnogene abeparvovec-xioi (Zolgensma), an SMN1 gene replacement, and Risdiplam (Evrysdi), a small molecule SMN2 modifier. To date, Gunther et al.performed the largest prospective study of the longest observational period of nusinersen therapy in adult patients with SMA [8]. The results demonstrate sustained efficacy across the phenotypic spectrum of adult.

SMA shows stabilization or improvement in motor function in a large number of patients, which is different from the natural history of the disease. By using the SMArtCARE registry dataset, consistent standards of care can be assumed since data came from experienced centers with specifically trained staff.

There are some limitations in the study since the use of uniform scales in all patients makes it difficult to capture small motor function changes in individual cases. Onasemnogene abeparvovec-xioi (Zolgensma), an SMN1 gene replacement, has given positive results in SMA children and is in observational trial SMART in children up to 21 kg. A combination of gene therapy trials with Nusinersen is an approach so far not explored since discontinuation of Nusinersen is done in the Zolgensma trial.

3. Advances on Dystrophinopathies

Dystrophinopathies are x-linked muscular diseases that emerge from mutations in the Dystrophin gene, including Duchenne and Becker muscular dystrophy. To address DMD, a disease-modifying approach must have the following potentials to be an ideal agent, (i) Amelioration of inflammation and fibrosis due to lack of dystrophin and (ii) regeneration of muscle stem cells and their maturation towards functional muscle cells that should reflect in terms of improved muscle strength.

The gold-standard and recommended therapy for DMD patients is based on glucocorticoids (prednisone, prednisolone, and deflazacort), which target the glucocorticoid receptor (GR) to exert the anti-inflammation effects by suppressing the NF-κB signaling pathway. However, DMD interconnects with bone loss and osteoporosis, which are exacerbated by glucocorticoid therapy.

In DMD glucocorticoids are usually administered in daily or intermittent doses; however, glucocorticoids have different efficacies and remarkable side effects, including weight gain, osteoporosis, cataracts, hypertension, and stunted bone growth. Bonifati et al. [9] found that the 1220 A to G (Asn363Ser—N363S) polymorphism in the steroid receptor has a definite modulating effect on steroid response in DMD patients by inducing a long-term sensitivity to glucocorticoids.

In a randomized double-blind controlled trial, 28 DMD patients were treated [10] with either deflazacort (DF) 2.0 mg/kg or placebo on alternate days. After 6 months of therapy, the deflazacort group significantly progressed in climbing stairs, rising from a chair, Gower's maneuver, and walking times.

Moreover, these motor outcomes continued to improve during a two-year follow-up. Additionally, the loss of ambulation of the deflazacort group was delayed for 12.7 months compared to placebo. This study lasted over 3 years using DF every other day, DF lasts in the body between 12 and 36 h. DF has been used in several DMD trials. A clear efficacy picture emerges from the FOR-DMD trial [11] where 196 DMD boys were randomized and 164 completed the trial. Both daily prednisone and daily DF were more effective than intermittent prednisone for the primary outcome.

Currently, vamorolone, an innovative steroid, is being investigated as a potential alternative to glucocorticoids and mineralocorticoids, aiming at maintaining the corticosteroids' efficacy profile while diminishing their side effects [12,13].

It should be recognized that DMD is a severely progressive disorder, with markedly decreased life expectancy and marked disability along the course. Postponing consistently the critical step of deambulation loss is indeed a major achievement that reflects in a better quality of life, and higher social and educational achievements, although other therapeutic approaches will be needed in a coordinated way to cure this disorder. Givinostat, a histone deacetylase (HDAC) inhibitor, is currently in development as a treatment for DMD but its mechanism of action

could theoretically apply to other muscle disorders. Givinostat is designed to inhibit HDACs, which are enzymes that prevent gene translation by changing the 3-dimensional folding of DNA in the cell.

Mercuri et al. conducted a successful multicentre, randomized, double-blind, placebo-controlled, phase 3 trial with Givinostat at 41 tertiary care sites in 11 countries. EPIDYS, a randomized, double-blind, placebo-controlled, multicenter study, included 179 ambulant male individuals who were randomly assigned 2:1 to either oral givinostat or placebo for an 18-month treatment period. Of these, 120 boys formed the target population. Eligible DMD was ambulant, male, and aged at least 6 years, had a genetically confirmed diagnosis, completed two four-stair climb assessments with a mean of 8 s or less, had a time-to-rise of at least 3 s but less than 10 s, and had received systemic corticosteroids for at least 6 months. DMD boys were randomly assigned (2:1) to receive either oral givinostat or a matching placebo twice a day for 72 weeks, stratified by concomitant steroid use.

The dose was flexible, based on weight, and was reduced if not tolerated. After this trial givinostat received FDA approval. After the study, results showed a slower decline in givinostat-treated patients on the primary endpoint of climbing 4 stairs in comparison with placebo. The FDA accepted the new drug application (NDA) submission for givinostat, with data from the phase 3 EPIDYS trial (NCT02851797) as the supporting evidence.

Becker muscular dystrophy (BMD) is caused by dystrophin deficiency due to inframe deletions, duplications, or variants in the dystrophin gene. It has onset usually in adolescence, usually by 12 years. Despite onset, independent walking is never lost before the third decade; BMD is slowly progressive with phenotypic variability and can present different clinical signs such as waddling gait, and exercise-related cramps with or without myoglobinuria and cardiomyopathy as clinical features with variable evolution. In a series of cases followed for over twenty years, a multifactorial treatment regimen was followed [14]. The steroid treatment has been personalized for individual cases. Early treatment of cardiomyopathy with ACE inhibitors is recommended and cardiac transplantation was of benefit in cases with good mobility. Management includes multidisciplinary care with physiotherapy to reduce joint contractures and prolong walking.

Personalized treatments are required for individual cases and in the future might include vamorolone, which has been approved by EMA.

That's in contrast to the progressive deterioration of motor function seen during the natural course of BMD in the absence of treatment. Gene therapy in DMD is controversial The full DMD gene is too large to fit in an adeno-associated virus vector. In 2023, Sarepta Therapeutics sought accelerated approval for delandistrogene moxeparvovec (SRP-9001), an adeno-associated virus gene therapy for Duchenne muscular dystrophy. SRP-9001 codes for a shortened version of dystrophin ("microdystrophin") that is distinct from any of the shortened forms of dystrophin found in Becker muscular dystrophy. After FDA leadership strongly encouraged flexibility, the FDA granted SRP-9001 accelerated approval in June 2023 (under the brand name Elevidys) for a sub-group of boys with Duchenne muscular dystrophy [15]. However, clinical results appeared to influence this approval. Study 102 was a randomized trial of 41 boys aged 4 to 7 years. At week 48, the change in the primary outcome, North Star Ambulatory Assessment (NSAA) score, was not statistically significantly different for SRP-9001 compared with placebo. The change in NSAA score for younger boys was greater with treatment than with placebo (4.3 vs. 1.9), but statistical testing is not meaningful in this post hoc analysis. Older boys had numerically worse changes with SRP-9001 than with placebo (−0.2 vs. 0.5).

4. LGMD's Current Progress and Gene Therapy

In addition to molecular-based therapies, such as steroids many non-specific muscular dystrophy therapies are currently in clinical trials. Such approaches may prove beneficial for LGMD. These include targeting the myostatin pathway, muscle inflammation, regeneration, or fibrosis. Recently completed early-phase studies of non-specific therapies in LGMD include an anti-myostatin drug to improve muscle growth (NCT02841267), a steroid to target inflammation (NCT00527228), and a tRNA synthetase to target muscle inflammation and regeneration (NCYT02836418).

Recent developments in our genetic understanding of LGMD and molecular approaches to therapy have led to proposed gene replacement therapies for at least three LGMD mutations. Phase 1 studies of AAV-delivered gene therapy for LGMD 2C/R3 and D/R6 (sarcoglycan) have demonstrated proof-of-principle for delivery in an isolated muscle and showed sarcoglycan staining in muscle biopsies post-therapy [16,17]. Preclinical efforts to develop gene therapies for FKRP mutations (LGMDR9) and sarcoglycan B mutations (LGMDR4) are underway [18–25]. For the dominant LGMDs which are not amenable to gene replacement, there is evidence that small molecules can affect the pathology associated with DNAJB6 mutations (LGMDD1) [26]. With multiple gene replacement therapies currently in pre-clinical/phase 1 testing, there is a demand for natural history data to guide trials.

The use of ribitol supplementation is on the way in the UK in LGMD R9 and has a large patient request and consensus.

5. ERT Advancement in Glycogenosis Type 2

Glycogenosis type 2 (GSD2) is a rare autosomal disorder caused by a deficiency of alpha-glucosidase, a lysosomal enzyme that hydrolyzes glycogen to glucose. Its pathological features include vacuolar myopathy, with detrimental autophagosome accumulation resulting in muscle autophagic degeneration. Since 2006, both infantile (classic Pompe disease or PD) and late-onset Pompe Disease (LOPD) patients have been treated, various double-blind or observational studies including large cohorts of LOPD have recently found that ERT is effective in modifying the natural course of the disease [27]. Most LOPD cases show an improvement in the first 24 months in the six-minute walk test (6 MWT); vice versa, untreated patients do not show 6MWT improvement over time. ERT with alglucosidase alpha represents an effective treatment for PD and LOPD, ERT positively affects muscle strength, pulmonary function, and daily life activities in LOPD. Maximal ERT efficacy with al-glucosidase was observed in the first two to three years, then it declined [28]. Recently avalglucosidase with improved alpha M6P-receptor targeting and enzyme uptake was approved by both FDA and European regulatory agencies.

Pathophysiologic aspects such as enzyme tissue entry, autophagy, and the response to ERT treatment of motor and respiratory components are considered important [29,30]. This new ERT might improve QoL for GSD2 patients. There has been an important impulse to research various aspects of the disease about both the role of autophagy and the immune adverse events, avalglucosidase alpha might be a further step forward. Prospects of ERT include the use of the new avalglucosidase alfa with improved M6P-receptor targeting and enzyme uptake is underway [31].

In the COMET Phase III trial as the primary endpoint was chosen respiratory muscle function, measured by upright forced vital capacity (FVC) % predicted. Secondary endpoints were endurance and 6MWT, which improved by about 30 m, which for patient walking might represent the ability to do a cross-walk [32]. In an extension study, improvements were confirmed in the group that switched to NeoGAA [33].

One further strategy to improve ERT is to use enzyme stabilizers to modulate GAA enzymatic activity with chaperone, this was first experimented for GSD2 with selected variants, adding a further strategy to Next Generation ERT (NG_ERT).

Different doses of the chaperone (50 to 600 mg) were studied in an open trial, showing a 1.2–2.8-fold increase in GAA activity [33]. In a phase 3 trial PROPEL combining cipaglucosidase alfa, plus miglustat 85 treated LOPD compared favorably to alglucosidase alpha plus placebo [34] and resulted in treatment approval in the EU. Minimal clinically important differences analysis favors both NG-ERT.

ERT might also be improved by combination with other drugs, exercise, and nutrition [35].

6. Advances in Mitochondrial Disorders

Mitochondrial diseases are extremely heterogeneous genetic disorders due to faulty oxidative phosphorylation. No cure is currently available for these conditions, besides supportive interventions aimed at relieving complications. Mitochondria are under a double genetic control carried out by the mitochondrial DNA (mtDNA) and by nuclear DNA. Thus, not surprisingly, mutations in either genome can cause mitochondrial disease. Although mitochondria are usually associated with respiration and ATP synthesis, they play fundamental roles in a large number of other biochemical, signaling, and execution pathways, each being a potential target for therapeutic interventions. These can be classified as general therapies, i.e., potentially applicable to several different mitochondrial conditions, or therapies tailored to a single disease, i.e., personalized approaches, such as gene therapy, cell therapy, and organ replacement. Mitochondrial medicine is a particularly lively research field, and the last few years witnessed a steady increase in the number of clinical applications A classical therapeutic approach to mitochondrial myopathies has consisted of using a cocktail with carnitine, coenzyme Q/Idebenone, and riboflavin supplement. Previous studies in patients with mitochondrial disease highlight the high prevalence of cognitive impairments, fatigue, depression, and a lower quality of life. Results underline the importance of screening for cognitive impairments by an increasing disease manifestation. Regarding fatigue, results of a study by van del Loo et al. [36] showed that almost 80% of the patients experienced severe fatigue. This is in line with previous studies in MD, reporting fatigue in 60–100% of the patients [37].

The relationship between biological and physiological factors remains complex. This study aims to investigate the status of and interrelationships between biological and physiological functioning, cognitive functioning as well as fatigue, depression, societal participation, health perceptions, and QoL.

Although there are different methods of nuclear gene editing, there are still no effective treatments against mitochondrial disorders due to genetic alterations. Now, a group of researchers at Precision Biosciences Inc. and the University of Miami has developed a genetic edition platform that targets mitochondrial DNA (mtDNA) to delete its mutations.

"The ARCUS technology that we use is based on an enzyme found in nature called I-CreI. It is an enzyme that recognizes a 22-base pair DNA sequence within a species of green algae. And when it finds that DNA sequence, it will generate double-strand breaks," authored by Wendy Shoop, a scientist at Precision Biosciences, told BioWorld [38].

7. Lipid Storage Myopathies and Beta-Oxidation Defects

Lipid storage myopathy (LSM) is agroup of inherited myopathy caused by gene mutation, which is pathologically characterized by abnormal lipid deposition in muscle fibers. The genetic characteristics of LSM are autosomal recessive inheritance. Some late-onset LSM patients can be dramatically resolved by riboflavin treatment, so this clinical phenotype is called riboflavin-responsive LSM (RR-LSM). Riboflavin, also known as vitamin B2, is a coenzyme of some important oxidoreductases in the body and participates in the energy metabolism process in mitochondria. Riboflavin supplements can help fat metabolism and thus achieve the purpose of treating RR-LSM. Therefore, early recognition of RR-LSM is crucial to improve the prognosis of patients.

8. Myotonic Dystrophy

DM1 is caused by a (CTG)n repeat expansion in the 3′-untranslated region of the DMPK gene located within chromosome band 19q13.3 This expansion may occur during gametogenesis and expand between generations. Normal individuals have between 5 and 35 CTG repeats. DMPK alleles containing over 35 CTG repeat units demonstrate a length-dependent risk of instability on transmission. Patients with between 36 and 50 CTG repeats are asymptomatic but are at risk of having children with larger, pathologically expanded repeats. Alleles containing a CTG-repeat with a length of 51–150 may be either asymptomatic or may give rise to minimal or classical DM1. A more severe DM1 phenotype is associated with DMPK alleles with sizes > 150 CTG-repeat units.

The core mechanism for DM1 is RNA toxicity, whereby DMPK transcripts with expanded CUG repeats form nuclear condensates that sequester splicing factors in the Muscleblind-Like (MBNL) family. The resulting loss of MBNL function causes misregulation of alternative splicing and other changes in RNA processing.

DM2 is caused by a tetranucleotide (CCTG)n repeat expansion in the first intron of the CCHC-type zinc finger nucleic acid binding protein (CNPB) gene. The repeat expansion for DM2 is much larger than for DM1, ranging from 75 to over 11,000 repeats. Unlike DM1, the size of the repeated DNA expansion does not correlate with age of onset or disease severity.

The use of mexiletine for myotonia has been found effective and validated in DM1 and also in nondystrophic myotonia by Statland et al. [39] with few precautions for possible cardiac complications.

In a recent experimental study in a mouse model, the use of verapamil has been found effective [40] one has, however, to remember the frequent cardiac rhythm involvement in many DM1 cases, previous trials in DMD had negative effects because calcium antagonists caused a pseudo-infarct EKG syndrome.

Several strategies have been developed to reduce the effects of DM pathogenesis. These approaches are being investigated in animal models and in vitro, but not yet in clinical trials.

Antisense oligonucleotides (ASOs) have demonstrated particularly promising results in removing CUG exp RNA and reversing downstream toxic consequences in both DM1 patient cells and animal models.ASOs target the RNA through base pairing to complementary nucleotide sequences. Natural nucleotides are not suitable for therapeutic application because of their sensitivity to cellular nucleases. Various chemical modifications have significantly improved the stability and binding affinity of ASOs such as phosphorothioate (PS) or phosphorodiamidate morpholino (PMO).

Much translational research is still needed to bring this experimental practice into clinical use, however, Dyne Therapeutics has announced positive initial data from his phase 1/II trial ACHIEVE assessing agent DYNE-101investigational antisense oligonucleotides in DM1 cases. DYNE-101 is a TfR1-targeting antigen-binding fragment conjugated to a gapmer ASO that targets nuclear DMPK RNA. Data show that DYNE-101 reduces mutant DMPK RNA, and foci formation, and corrects splicing defects in preclinical models of DM1, suggesting a potential effect in individuals with DM1. They achieved both a satisfactory safety profile and dose-dependent skeletal muscle delivery. In a planned trial with intravenous subministration every eight weeks for one ear to patients from 16 years to 65 years the primary endpoint will be a video hand opening time(vHOT), and key

secondary endpoint measurement of grip strength while other secondary endpoints are quantitative muscle testing (QMT) total score, and activities of daily living as measured by DM1-Activ, QoL.

Avidity Biosciences, Inc. (Nasdaq: RNA), a biopharmaceutical company committed to delivering a new class of RNA therapeutics called Antibody Oligonucleotide Conjugates (AOCs™), announced that the U.S. Food and Drug Administration has granted Breakthrough Therapy designation to delpacibart etedesiran (AOC 1001, del-desiran), for the treatment of DM1 as an investigational treatment designed to address the root cause of DM1. Avidity recently reported positive long-term MARINA-OLE™ data demonstrating reversal of disease progression in adults living with DM1 across multiple endpoints including vHOT, muscle strength, and DM1-Activ when compared to natural history data

Avidity is initiating the global pivotal HARBOR™ study of del-desiran. The primary endpoint in the Phase 3 HARBOR trial is vHOT and key secondary endpoints include muscle strength as measured by hand grip strength and quantitative muscle testing (QMT) total score, and activities of daily living as measured by DM1-Activ.

9. Facioscapulohumeral Dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common myopathies in adults, displaying a progressive, frequently asymmetric involvement of a typical muscle pattern. FSHD is associated with epigenetic derepression of the polymorphic D4Z4 repeat on chromosome 4q, leading to DUX4 retrogene toxic expression in skeletal muscles.

Loposmapimod a Dux4 inhibitor was evaluated in phase 1 trial [41]. Although primary endpoints in gene expression weren't met, potential improvements in muscle structure and function were found and might be promising.

Identifying biomarkers that correlate with disease severity would facilitate clinical management and assess potential FSHD therapeutics' efficacy. Gros et al. found an alteration of IL-6 cytokine [42] both in FSHD cases and animal models, this was replicated in a study.IL-6 was identified as the only cytokine with a concentration correlating with several clinical severity and functional scores, including Clinical Severity Score, Manual Muscle Testing sum score, and Brooke and Vignos scores. Further, FSHD patients displayed overall IL-6 levels more than twice as high as control, and patients with milder phenotypes exhibited lower IL-6 serum concentration than those with severe muscular weakness. FSHD-like mouse model analysis confirmed that IL-6 levels positively correlate with disease severity and DUX4 expression.

On this basis a clinical trial is in preparation to reduce the Il-6 level in FSHD, one has to consider that inflammatory infiltrates in FSHD biopsies are focal and scanty and do not explain further disease course or progression. Another approach is to anti-DUX strategy here again the fact that the action of this gene is mostly in early life will need to identify other strategies to antagonize FSHD progression.

10. Advances in Drug Available for Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder that affects the postsynaptic neuromuscular junction and is characterized by fluctuating weakness of focal or generalized skeletal muscles. In severe cases, it can cause respiratory failure. Approximately 80% of patients with MG has anti-acetylcholine receptor (AChR) antibodies [2]. The symptoms of generalized MG can significantly affect daily functioning, work activities, and the overall QoL, including socio-economic aspects. Therapy for MG includes rescue therapy for acute crises, and long-term immunomodulatory therapy aimed at reducing disability and disease activity. Fast-acting treatments including steroids, intravenous immunoglobulin (IVIg) administration, and plasma exchange, are employed as rescue therapies. However, long-term management involves the use of oral corticosteroids and immunosuppressive drugs, such as azathioprine, and mycophenolate mofetil [43].

Early diagnosis and the availability of effective treatments have reduced the burden of high mortality and severe disability previously associated with MG. Consequently, the prognosis of MG is now much improved. However, despite extensive knowledge of MG and its etiology, diagnosing MG remains problematic and can be delayed because of its nonspecific and fluctuating symptoms, and the management of MG is associated with considerable limitations. Current treatments based on immunomodulation are associated with adverse effects arising from prolonged immune suppression. New drugs in addition to steroids. such as cyclosporine A (CSA) were evaluated in nine MG patients [44]: the cases were 16–63 years old, with a diagnosis of severe MG with about 2 years of disease duration. All the patients had been previously treated either with corticosteroids or by combined azathioprine immunotherapy, and five needed periodic plasma exchange. During CSA treatment seven of nine patients improved their muscle strength and functional score: the reduction of plasmapheresis cycles in the five patients who needed periodic plasma exchange to maintain an acceptable QoL showed a valuable cost-benefit

analysis. In all the patients except one the steroid dosage was reduced and in seven of the nine patients, the dose reduction was over 50% with subsequent reduction of the steroid side effects.

The side effects were a serum creatinine increase in the first year of therapy, hypertrichosis, gingival hyperplasia present in four patients, and high blood pressure in one. CSA treatment may be a valuable add-on.

Complement has a role in refractory generalized myasthenia gravis [2], but no previous approved therapies specifically targeted it, before eculizumab which binds to the C5 terminal fraction. A multicentre trial was done by Howard et al. [45] to evaluate the safety and efficacy of eculizumab in anti-AChR antibody-positive refractory generalized MG (REGAIN), eligible patients were at least 18 years old, with an MG-Activities of Daily Living (MG-ADL) score of at least 6 or more, and received vaccination against Neisseria meningitides. They had previously been treated with two immunosuppressive drugs or one immunosuppressive drug and chronic IVIg or plasma exchange for one year with no response. Those with a history of thymoma or thymectomy, use of IVIg or plasma exchange 1 month before randomization, or rituximab within 6 months, were excluded. Trial participants were assigned to either intravenous eculizumab or intravenous matched placebo for 26 weeks. Eculizumab was subministered at a dosage of 900 mg in the first 3 weeks; 1200 mg at week 4; and 1200 mg given every fortnight thereafter as a maintenance dose. If possible, patients were maintained on existing MG therapy, rescue medication was done according to the physician's decision. The safety analyses included all randomly assigned patients who received eculizumab or placebo. REGAIN trial was registered with ClinicalTrials.gov, number NCT01997229.

Between 2014 and 2016, 125 patients, 62 with eculizumab and 63 with placebo were treated. The primary analysis showed no significant difference between eculizumab and placebo deaths or cases of meningococcal infection that occurred. The most common adverse events in both groups were headache and upper respiratory tract infection, in the placebo group 12 cases required rescue therapy.

Eculizumab was well tolerated. Since the secondary and sensitivity analysis results were inconsistent with the primary endpoint outcome; further research into the role of complement was needed by a post-intervention study led by Mantegazza [46].

The latest option for MG patients came when the FDA approved a new targeted therapy, efgartigimod that is aimed at people with generalized MG. Intravenous efgartigimod alfa, known as efgartigimod alfa-fab (Vyvgart) is the first neonatal Fc receptor antagonist approved in several countries worldwide, including the USA and EU for the treatment of generalized MG. In the double-blind, placebo-controlled phase 3 ADAPT trial in patients with MG, efgartigimod alfa significantly and rapidly reduced disease burden and improved muscle strength and QoL [47]. Several monoclonal antibodies and new drugs represent a breakthrough in MG care and this illustrates how applying basic science discoveries to the root causes of neuromuscular disease can lead to new treatment approaches.NMD670—a ClC-1 inhibitor compound—could restore neuromuscular function "leading to clinically meaningful effects" in patients with MG.

11. Charcot-Marie-Tooth (CMT) Disease

Therapy availability seems possible within the next few years for metabolic neuropathies like CMT-SORD [48]. This malfunction results in increased sorbitol levels, which ultimately leads to a predominantly motor neuropathy. A promising approach is to use drugs inhibiting aldose reductase, which converts glucose into sorbitol and acts before the SORD-mediated step, to reduce the production of sorbitol. SPTLC1/2-HSN1848), where correction of the biochemical defect may be achieved: SPTLC1/2 mutations cause serine-palmitoyltransferase to develop a higher affinity for alanine and glycine than for serine in the sphingolipids' synthesis pathway, leading to the production of neurotoxic deoxysphingolipids.

Unfortunately, despite preclinical data suggesting that L-serine supplementation reduces deoxy sphingolipid levels, a pilot trial on 18 patients did not meet its primary endpoint, probably due to the small sample size [49]. For other forms of CMT, this goal seems to be more distant, with the greatest advancement expected in CMT1A by PMP22 silencing within the next five years, as phase I/IIa trials are planned.

Recent success in the treatment of transthyretin-related amyloidosis offers promising possibilities for progress in this field, mainly driven by technological advancements. However, PMP22 downregulation needs to be strictly controlled, as an overly excessive reduction poses the risk of developing hereditary neuropathy with liability to pressure palsy (HNPP).

It remains crucial to refine clinical trial design, as certain treatments might not meet the clinical endpoints, but they could prove effective when employing more responsive surrogate measures, such as blood biomarkers and quantitative muscle MRI to accurately assess denervation-related fat fraction. The CMT research community is working on developing responsive surrogate biomarkers that correlate with clinical disability and predict clinical outcomes.

12. Conclusions

Researching rare neuromuscular disorders is challenging due to the heterogeneity of disease presentations from multi-systemic organ presentation to impacting specific groups of cells or tissues. Furthermore, most of these diseases face several limitations: large heterogeneity of patient presentation, incomplete penetrance, lack of natural histories, or scarcity of patients. Indeed, neuromuscular disorders constitute a diverse group of diseases that impact nerves and/or muscles, resulting in various clinical manifestations including, but not limited to, delayed motor function, muscle weakness and atrophy, and movement impairments. The field has beneficiated from all the recent and significant advancements in genomics (with the continuous advancement of sequencing technologies), stem cell biology (with the creation of new cellular models through the generation of induced pluripotent stem cells), and molecular biology (with the emergence of gene and RNA editing technologies). Specifically, most of these diseases can access or obtain multi-omics data, thanks to high throughput sequencing technologies, enabling a comprehensive analysis of these diseases like never before and paving the way for the emergence of innovative and targeted therapeutic approaches. Undeniably, the marketing of orphan drugs (drugs specifically designed for a rare condition) suffers greatly from insufficient research and funding to provide the understanding and knowledge to adequately address these unmet medical needs. Thus, pharmacotherapies typically remain the treatment of choice but are rarely specific and can elicit numerous adverse effects. However, with the advent of promising technologies such as gene transfer or gene and RNA editing, personalized and precise medicine appears to be attainable for a substantial subset of these disorders. This review aims to highlight advances in different aspects focusing on different diseases exploring the challenges and hopes of this highly dynamic field of research from drug discovery to clinical trials.

Cost-effectiveness is an important consideration: while the use of ERT both with old and next-generation ERT is not cost-effective preventing their use in several countries, like Chile, carnitine or riboflavin supplementations are giving excellent results in the realm of FAOD. Similar considerations apply for new drugs in MG where several are pending approval from competent authorities like the use of several monoclonal antibodies for their excessive cost. Similarly, cost is also an issue that cannot be ignored. Sarepta Therapeutics has priced Elevidys at $3.2 million for DMD gene therapy. This is an enormous price tag for a therapy that has failed to meet its primary endpoint in the 2 randomized trials in which it has been studied and that is not curative. Curative gene therapies for neuromuscular disorders affecting young children can be extremely valuable and worth very high prices. The Institute for Clinical and Economic Review felt that Zolgensma, a gene therapy for spinal muscular atrophy, could be worth up to $2.1 million and that it would be a possible improvement in younger children, while studies are ongoing on its possible use in children with age up to 21 kg.

Neuromuscular diseases are a group of conditions that affect muscle metabolism and neuromuscular junction, leading to a wide range of physical and functional impairments. These disorders can have a significant impact on the quality of life for patients, often resulting in debilitating symptoms and limited mobility. However, advancements in medicine, particularly the development of new drugs and technologies examined, have the potential to transform the lives of neuromuscular patients. The introduction of new drugs has opened up possibilities for better symptom management, helping patients maintain a higher quality of life.

Another useful approach that appears for proximal myopathy cases is the use of a wearable device of the weight of half a kg (exoBand-Mov, Exo-ANKLE Moveo) which is of practical use both for proximal or distal myopathies, CMT, and multiple sclerosis patients.

It is essential to note that while some of these treatments have shown promising outcomes in clinical trials, they may not be widely available or approved for routine use. Consulting with healthcare professionals and seeking expert medical advice is crucial when considering any specific neuromuscular treatment. For instance, in dystrophinopathies, different drugs resulted in different outcomes and narratives for patients and caregivers. This raises questions about how and when people with chronic neuromuscular diseases should be informed on new available treatments. Both LOPD and steroid-resistant MG patients have poor QoL despite several available treatments. We recommend that health professionals find a way to carefully balance guidance and information about experimental medicine, including the fact that experimental drugs sometimes fail, or do not work as well as hoped for, or do not become available, while still sustaining patients' hopes for their future.

Conflicts of Interest

The author declares no conflict of interest.

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