

New Treatments Available in Neuromuscular Disorders

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1. Introduction

Neuromuscular diseases cover a wide range of acquired and inherited myopathies, metabolic myopathies, and neuro muscular junction disorders. For most of them, treatment options 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 more effective diagnostic tools, such as modern imaging techniques, histopathological studies, advanced genetics, and a better in-depth understanding of their underlying pathomechanisms has led to an earlier diagnosis and improved therapeutic opportunities¹.

Recent developments in novel therapies for neuromuscular diseases offer new perspectives on patient management. This review examines how the emergence of new therapies impacts the quality of life (QoL) of parents and children with Duchenne muscular dystrophy or glycogenosis type 2, two genetic neuromuscular disorders, characterized by progressive muscle degeneration.

In adult-onset Glycogenosis type 2 Neo GAA 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 extension.

Neo GAA 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. Myasthenia Gravis (MG) is the most common neuromuscular transmission disorder². 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. The use of cyclosporin and eculizumab has changed the patient's perspective. MG patients are benefitting from an expansion of treatments and more therapies are in the pipeline. Novel drugs are increasingly used to target specific molecules involved in neuromuscular diseases. For example, nusinersen³ and risdiplam have been developed to target RNA splicing defects in SMA⁴. Similarly, other targeted therapies are being explored for diseases like myasthenia gravis, and muscular dystrophies.

Viewpoint on Dystrophinopathies are x-linked muscular diseases that emerge from mutations in the Dystrophin gene, including Duchenne and Becker muscular dystrophy. QoL has been studied in DMD⁵, more severe in natural course and evolution. It is also important to evaluate the caregiver's role. In a cohort of 502 people including Duchenne, Becker patients, or Limb-Girdle Muscular Dystrophy key relatives, Magliano⁶ reported that, despite the difficulties associated with caregiving, relatives identify valuable benefits in their experience. 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 efficacy and remarkable side effects, including weight gain, osteoporosis, cataracts, hypertension, and stunted bone growth. Bonifati⁷ found that the 1220 A to G (Asn363Ser - N363S) polymorphism in the gene 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 treated⁸ with either deflazacort 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.

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 hours. Deflazacort (DF) has been used in several DMD trials. A clear efficacy picture emerges from the FOR-DMD trial⁹ where 196 DMD boys were randomized and 164 completed the trial. Both daily prednisone and daily deflazacort 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^{10,11}. Ataluren was approved in several countries for DMD therapy¹². Ataluren (Translarna) is a molecule for stop codon read-through therapy, which could help up to 10-15% of DMD patients carrying nonsense mutations plus those carrying out frame mutations.

However, there is no pharmacological drug that can compensate for the lack of dystrophin in muscle fibers and open trials are undergoing with Ataluren to evaluate the real benefits of this subtype of DMD with stop-codon, is possible that some mutations might be more benign. Patients affected by DMD gene stop-codon-creating point mutations have been chronically treated with ataluren since EMA and AIFA conditional approval, however, there has been a halt on this treatment, since recently a European agency doubted its efficacy.

Becker muscular dystrophy (BMD) is caused by dystrophin deficiency due to in frame 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 followed¹³. 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. Viewpoint on 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 auto phagosome accumulation resulting in muscle auto phagic 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 disease¹⁴. Most LOPD cases show an improvement in the first 24 months in a 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 (14). 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^{15,16}. 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 underway¹⁷.

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 meters, which for patient walking might represent the ability to do a cross-walk¹⁸. In an extension study, improvements were confirmed in the switch group¹⁹.

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. 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 activity²⁰. In a phase 3 trial PROPEL combining cipaglucosidase alfa, plus miglustat 85 treated LOPD compared favorably to alglucosidase alpha plus placebo²¹ and resulted in treatment approval in the EU.

ERT might also be improved by combination with other drugs, exercise, and nutrition²². Advances in 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) antibodies². 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^{2,23}.

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 patients²⁴. 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 gravis², but no previous approved therapies specifically targeted it, before eculizumab which binds to C5 terminal fraction. A multicentre trial was done by Howard, et al.²⁵ 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 6 or more, and received vaccination against *Neisseria meningitidis*. 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 sub ministered 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 Clinical Trials.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 Mantegazza²⁶.

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 QoL²⁷. 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.

2. Conclusions

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 conclude that health professionals must find a way to carefully balance guidance and information about experimental medicine, including the fact that experimental drugs sometimes fail, do not work as well as hoped for, or do not become available, while still sustaining patients' hopes for their future.

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