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Advances and new treatments are available for neuromuscular disorders and affect Quality of Life.

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Abstract

Advances over the past two decades in the field of neuromuscular disorders have transformed the treatment landscape, bringing more genetic testing for screening, better laboratory analyses, new innovative therapies that target specific disease pathways and mechanisms, and a multidisciplinary approach to care. These advancements have led to more precise diagnoses and advances in the management of neuromuscular conditions, which can be life-altering for patients. This review examines how the emergence of new therapies impacts the quality of life (QoL) of parents and children with Duchenne muscular dystrophy and patients with late-onset glycogenosis type 2. Myasthenia Gravis (MG) is the most common neuromuscular transmission disorder. Despite the existence of few refractory cases, the goal of treatment is the complete remission of symptoms, achieved by thymectomy, immunosuppression, IVIG, or monoclonal antibody. Advances over the past two decades have been substantial both in mitochondrial disorders and for.MG patients that are benefitting from an expansion of treatments since more therapies are available.

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Keywords: deflazacort, vamorolone, acid alpha-glucosidase deficiency; enzyme replacement therapy; myasthenia gravis, cyclosporin, eculizumab, mitochondria.

Introduction

Neuromuscular diseases cover a wide range of acquired and inherited myopathies, metabolic myopathies,mitochondrial and neuromuscular junction disorders. For most of them, treatment options were,until recently, extremely poor or even non-existent, and often recommendations have beenlimited 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 opportunities (1).

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 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 extension.

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. 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. 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, nusinersen (3) and risdiplam have been developed to target RNA splicing defects in SMA (4). Similarly, other targeted therapies are being explored for diseases like myasthenia gravis, mitochondrial diseases and muscular dystrophies.

Advances on Dystrophinopathies

Dystrophinopathies are x-linked muscular diseases that emerge from mutations in the Dystrophin gene, including Duchenne and Becker muscular dystrophy.

They are a group of neuromuscular diseases in which psychological problems affect negatively the quality of life (QoL) not only patients but also caregivers.

QoL has been studied in DMD (5), 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, Magliano (6) 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. Bonifati (7) 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 treated (8) 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 trial (9) 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 therapy (12). 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. 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, higher social and educational achievements, although other therapeutic approaches will be needed in a coordinated way to cure this disorder.

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 (13). 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, that has been approved by EMA. Weeks before a decision was expected to be made for Italfarmaco's investigational agent givinostat, the FDA informed the company it has extended the review process, with a new scheduled PDUFA of March 21, 2024. Givinostat, a proprietary histone deacetylase (HDAC) inhibitor, is currently in development as a treatment for Duchenne muscular dystrophy (DMD), a severe neuromuscular genetic disease.

The FDA accepted the new drug application (NDA) submission for givinostat earlier this year, with data from the phase 3 EPIDYS trial (NCT02851797) as the supporting evidence. Givinostat is designed to inhibit HDACs, which are enzymes that prevent gene translation by changing the 3-dimensional folding of DNA in the cell. In the latest update, Italfarmaco noted that the agency needs more time to review the application, but that there were no issues with the data submitted.

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. At the conclusion of the study, results showed a slower decline in givinostat-treated patients on the primary end point of climbing 4 stairs in comparison with placebo (difference, 1.78 seconds; P = .0345).

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 (14). 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 underway (17).

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-walk (18).In an extension study, improvements were confirmed in the switch group (19).

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 activity [20]. In a phase 3 trial PROPEL combining cipaglucosidase alfa, plus miglustat 85 treated LOPD compared favorably to alglucosidase alpha plus placebo [21] and resulted in treatment approval in the EU.

ERT might also be improved by combination with other drugs, exercise, and nutrition (22).

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 (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 patients (24): 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 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 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 (26).

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 (27). 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.

Advances in mitochondrial disorders and QoL

Mitochondrial diseases are extremely heterogeneous genetic disorders due to faulty oxidative phosphorylation. No cure is currently available for these conditions, beside 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 a number of 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. Previous studies in patients with a 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 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 (29)

The relationship with biological and physiological factors remains complex. The aim of this study is 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.(30)

Conclusions

Conducting research on rare neuromuscular disorders is challenging due to the heterogeneity of diseases 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), in stem cell biology (with the creation of new cellular models through the generation of induced pluripotent stem cells) and in molecular biology (with the emergence of gene and RNA editing technologies). Specifically, most of these diseases have the ability to 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) suffer 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. In this special review I aimed to highlight advances in different aspects focusing on different diseases but exploring the challenges and hopes of this highly dynamic field of research from drug discovery to clinical trials.

Neuromuscular diseases are a group of conditions that affect the 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. This review explores the relationship between the quality of life and the introduction of new drugs for individuals with neuromuscular diseases.

Neuromuscular diseases often cause symptoms such as muscle weakness, and fatigue. The introduction of new drugs has opened up possibilities for better symptom management, helping patients maintain a higher quality of life.

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.

Declarations

Conflict of Interest

The Author declares that there is no conflict of interest.

References

1. Margeta M. (2023), Neuromuscular disease:2023 update.Free Neuropathology 4:2 (2023 doi: https://doi.org/10.17879/freeneuropathology-2023-4682

2.Angelini C (2011) Clin Drug Investig. Diagnosis and management of autoimmune myasthenia gravis.31(1):1-14. Doi: 10.2165/11584740-000000000-00000.

3. Parente V, Corti S. (2018) Advances in spinal muscular atrophy therapeutics. Ther Adv Neurol Disord. 5;11:1756285618754501. doi: 10.1177/1756285618754501. eCollection 2018.

4. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, Vuillerot C, Baranello G, Boespflug-Tanguy O, Goemans N, Kirschner J, Kostera-Pruszczyk A, Servais L, Gerber M, Gorni K, Khwaja O, Kletzl H, Scalco RS, Staunton H, Yeung WY, Martin C, Fontoura P, Day JW; SUNFISH Study Group(2022) Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomized, placebo-controlled trial.

Lancet Neurol. ;21(1):42-52. doi: 10.1016/S1474-4422(21)00367-7.PMID: 34942136

5.Orcesi S, Ariaudo G, Mercuri E, Beghi E, Rezzani C, Balottin U; SOLE NMDs Study Group (2014).A new self-report quality of life questionnaire for children with neuromuscular disorders: presentation of the instrument, rationale for its development, and some preliminary results. J Child Neurol. Feb;29(2):167-81. doi: 10.1177/0883073813511859. Epub 2013 Dec 18. PMID: 24352162

6. Magliano, M; Patalano,M.; Scutifero M; et al.(2015)Burden, professional support, and social network in families of children and young adults with muscular dystrophies.Muscle&Nerve 52:13–21.

7. Bonifati, D.M.; Witchel, S.F.; Ermani, M.; Hoffman, E.P.; Angelini, C.; Pegoraro, E.(2006) The glucocorticoid receptor N363S polymorphism and steroid response in Duchenne dystrophy. J. Neurol. Neurosurg. Psychiatry, 77, 1177–1179.

8. Angelini, C.; Pegoraro, E.; Turella, E.; Intino, M.T.; Pini, A.; Costa, C.(1994) Deflazacort in Duchenne dystrophy: Study of long-term effect. Muscle Nerve 17, 386–391.

9. Guglieri M., Bushby K, McDermott M.P, Hart K.A, Tawil R.,et al.(2022)
Effect of Different Corticosteroid Dosing Regimens on Clinical Outcomes in Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA 19;327(15):1456-1468.
doi: 10.1001/jama.2022.4315.

10. Smith, E.C.; Conklin, L.S.; Hoffman, E.P.; Clemens, P.R.; Mah, J.K.; Finkel, R.S.; Guglieri, M.; Tulinius, M.; Nevo, Y.; Ryan, M.M.; et al.(2020) Efficacy and safety of vamorolone in Duchenne muscular dystrophy: An 18-month interim analysis of a non-randomized open-label extension study.PLoS Med. , 17, e1003222.

11.Guglieri, M.; Clemens, P.R.; Perlman, S.J.; Smith, E.C.; Horrocks, I.; Finkel, R.S.; Mah, J.K.; Deconinck, N.; Goemans, N.; Haberlova, J.; et al.(2022) Efficacy and Safety of Vamorolone vs Placebo and Prednisone among Boys with Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA Neurol., 79, 1005–1014.

12. Bushby, K, Finkel R, Wong B, FOR THE PTC124-GD-007-DMD STUDY GROUP (2015) Ataluren treatment of patients with nonsense mutation dystrophinopathy Muscle &Nerve,50, 4,477-487.

13. Angelini, C, Marozzo R, Pegoraro V (2019) Current and emergent therapies in Becker Muscular Dystrophy (BMD)Acta Myol. , 1;38(3):172-179.
https://mc03.manuscriptcentral.com/jerp

14. Schoser B, Stewart A, Kanters S, et al (2017) Survival and long-term outcome in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. J Neurol. ;264 (4):621–630.

15. Pena, L.D.M.; Barohn, R.J.; Byrne, B.J.; Desnuelle, C.; Goker-Alpan, O.; Ladha, S.; Laforêt, P.; Mengel, K.E.; Pestronk, A.; Pouget, J.; et al (2019) Safety, tolerability, pharmacokinetic pharmacodynamics and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-

onset Pompe Disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscul. Disord. , 29, 167–186.

16. Dimachkie, M.M.; Barohn, R.J.; Byrne, B.; Goker-Alpan, O.; Kishnani, P.S.; Ladha, S.; Laforêt, P.; Mengel, K.E.; Pena, L.D.; Sacconi, S.; et al.(2020) NEO1 and NEO-EXT studies: Long-term safety and exploratory efficacy of repeat avalglucosidase alfa dosing for 5.5 years in late-onset Pompe disease patients. Mol. Genet. Metab. , 129, S49.

17. Dimachkie, M.M., Barohn, R.J, Byrne, B. et al (2022) Long-term Safety and Efficacy of Avalglucosidase Alfa in patients With Late-Onset Pompe Disease Neurology;99:e536-e548. doi:10.1212/WNL.0000000000200746

18. Diaz-Manera, J.; Kishnani, P.S.; Kushlaf, H.; Ladha, S.; Mozaffar, T.; Straub, V.; Toscano, A.; van der Ploeg, A.T.; Berger, K.I.; Clemens, P.R.; et al (2021) Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): A phase 3, randomized, multicentre trial. Lancet Neurol. 20, 1012–1026.

19. Kishnani P, Diaz Manera J, Toscano A, et al (2023) Efficacy and Safety of Avalglucosidase Alfa in Patients With Late-Onset Pompe Disease After 97 Weeks: A Phase 3 Randomized Clinical Trial JAMA Neurol;80(6):558-567.doi: 10.1001/jamaneurol.2023.0552.

20. Parenti, G.; Fecarotta, S.; la Marca, G.; Rossi, B.; Ascione, S.; Donati, M.A.; Morandi, L.O.; Ravaglia, S.; Pichiecchio, A.; Ombrone, D.; et al. (2014) A Chaperone Enhances Blood -Glucosidase Activity in Pompe Disease Patients Treated with Enzyme Replacement Therapy. Mol. Ther., 22, 2004–2012.

21. Schoser, B.; Roberts, M.; Byrne, B.J.; Sitaraman, S.; Jiang, H.; Laforêt, P.; Toscano, A.; Castelli, J.; Díaz-Manera, J.; Goldman, M.; et al (2021) Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): An international, randomized, double-blind, parallel-group, phase 3 trial. Lancet Neurol. , 20, 1027–103

22. Angelini, C (2021) Exercise, nutrition, and enzyme replacement therapy are efficacious in adult Pompe patients: report from EPOC Consortium Eur J Transl Myol 3;31(2):9798.doi: 10.4081/ejtm.2021.9798.

23. Murai H, Utsugisawa K, Motomura M, Imai T, Uzawa A, Suzuki S. (2023) The Japanese clinical guidelines (2022) for myasthenia gravis and Lambert–Eaton myasthenic syndrome. Clinical and Experimental Neuroimmunology 14:19-27 https://doi.org/10.1111/cen3.12739

24. Bonifati DM, Angelini C (1997) Long-term cyclosporine treatment in a group of severe myasthenia gravis patients. J Neurol. ;244(9):542-7. doi: 10.1007/s004150050141.

25. Howard JF Jr, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, Jacob S, Vissing J, Burns TM, Kissel JT, Muppidi S, Nowak RJ; Brien F, Wang JJ, Mantegazza R; REGAIN Study Group. (2017). Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN): a phase 3, randomized, double-blind, placebo-controlled, multicenter study.Lancet Neurol. Dec;16(12):976-986.

26. Mantegazza R, Wolf G, Muppidi S, Wiendl H, Fujita PK; Brien LF, Booth EDH, Howard F Jr, REGAIN Study Group (2021) Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and its open-label extension. Neurology 96:e610-618 https://doi.org/10.1212/WNL.0000000000011207

27.Young-A Heo (2023) Efgartigimod Alfa in Generalised Myasthenia Gravis: A Profile of Its Use CNS Drugs.; 37(5): 467–473.

28. van de Loo, K.F,van Zeijl, N.T.,. Custers, J.A.E, Janssen M.C., Verhaak A C.M.(2022) conceptual disease model for quality of life in mitochondrial disease.Orphanet Journal of Rare Diseases volume 17, : 263

29. Mancuso M., Angelini C, Bertini E, et al. (2012)Fatigue and exercise intolerance in mitochondrial diseases. Literature revision and experience of the Italian Network of mitochondrial diseases,Neuromuscul Disord 22 Suppl 3(3-3):S226-9.doi: 10.1016/j.nmd.2012.10.012.

30. De Miguel,M.(2023)ARCUS gene editing tool repairs pathological mitochondrial DNA. Dec. 18.Bioword science.