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DRUG PROFILE

Evaluating avalglucosidase alfa for the management of late-onset Pompe disease

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ABSTRACT

Introduction: Glycogenosis type II (GSDII) is a rare autosomal disorder that is caused by the deficiency of alpha-glucosidase, a lysosomal enzyme that hydrolyzes glycogen to glucose. Autophagy dysregulation plays a critical role. Importantly, since 2006, both patients with infantile (classic Pompe disease) and adult GSDII (late-onset Pompe disease or LOPD) have been treated with enzyme replacement therapy (ERT). To support this use, several double-blind and observational studies including large cohorts of GSDII patients have been undertaken and have shown ERT to be effective in modifying the natural course of disease. Indeed, most LOPD cases improve in the first 20 months of treatment in a six-minute walk test (6MWT), while those who are untreated do not; instead, their response declines over time.

Areas covered: The author reviews avalglucosidase alpha, a therapy approved by both the FDA and European regulatory agencies. Herein, the author considers the pathophysiological approaches such as the role of enzyme entry, autophagy, and the response to ERT treatment of motor and respiratory components.

Expert opinion: There has been a notable drive toward the research of various aspects of this disease regarding the role of new enzyme penetration and immune adverse events. Consequently, avalglucosidase alpha might be a further step forward.

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Pompe disease; glycogenosis type 2; enzyme replacement therapy; autophagy; acid alpha-glucosidase

1. Introduction

Acid α-glucosidase (GAA) is an enzyme, known also as acid maltase, which is deficient in Glycogenosis type II (GSDII) (EC232300). After human skeletal muscle fractionation, it was found localized in lysosomal fraction and demonstrated that it has both α-1,4 and α-1,6 glucosidase activities and could thus degrade glycogen polysaccharide completely [1,2]. Defective GAA determines lysosomal accumulation of glycogen and subsequently of free cytoplasmic glycogen, while a lysosomal block leads to the cellular accumulation of autophagosomes [3,4]. GSD II presents across a spectrum of clinical phenotypes, that manifest in the severe infantile Pompe disease (PD) or the milder childhood type, to a relatively benign adult form. The activity of residual enzyme is absent in PD and variably decreased in childhood, and adult forms [1], in fibroblast culture is possible to demonstrate the adult form of GSD II [5]. The rate of GSD II progression appears inversely proportional to the presence of residual enzyme activity. It is somewhat schematic to use the onset before or after one year to differentiate PD from LOPD since a whole spectrum of clinical presentations has been described, more appropriate is to recognize infantile, childhood, juvenile adult, and late-onset GSD II forms. The classic infantile-onset form arises in the first months of life presenting with generalized muscle weakness, severe cardiomegaly, difficulty in feeding, a failure to thrive, and respiratory failure. Those children who are untreated children die within one year, primarily because of progressive cardiomyopathy and respiratory distress [6,7]. With juvenile forms of the GSDII, symptoms appear between 2 years and 5 years of age, and, in these instances, cardiomyopathy is seldom seen. Meanwhile, late-onset GSDII is characterized by progressive proximal and axial muscle weakness, leading to progressive loss of motor function, an altered posture, and the alteration of normal patterns of proximo-distal movement, a rigid spine and diaphragmatic weakness with respiratory insufficiency also frequent. There is rarely cardiac involvement reported in adult patients and is usually less severe than in infantile and juvenile patients, characterized by cardiac hypertrophy (involving the left ventricular wall or the interventricular septum), and conduction abnormalities. In late-onset patients who remain untreated, muscle strength and pulmonary function tend to deteriorate over the years, leading to eventual wheelchair use and respiratory support in the majority of cases.Limb-girdle and trunk muscles are typically affected in such cases also late-onset PD (LOPD), associated with respiratory insufficiency; other clinical features were described, such as limited exercise capacity and ptosis. In untreated LOPD, limb, and trunk muscle weakness progress and respiratory function decreases over the years, leading in several cases to respiratory support and lack of independent mobility [7–9]. A recent observational series reported that 14% of adult cases might present cardiac involvement, detected by echocardiography [10]. LOPD exhibit markedly reduced quality of life [11,12], and have high mortality with about 27 years survival after diagnosis [9]. Enzyme replacement therapy (ERT) was introduced with rhGAA in 2006 and led to variable motor improvement in LOPD, observational studies

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Article highlights

- In observational studies in adult GSD II, maximal efficacy with rhGAA was found in the first 24–36 months, and then it declined.
- Adverse events are relatively mild, and a rechallenge needs careful evaluation.
- Prospects of enzyme replacement therapy (ERT) include the improved enzyme preparation NeoGAA with larger tissue penetration.
- An evaluation of NeoGAA (avalglucosidase alfa) clinical trials is favorable regarding safety and has a positive outcome.
- Measurement of pulmonary capacity, as FVC percent, was chosen as the primary endpoint in the COMET 3 trial, rather than the 6MWT, and additional motor outcome measures such as GSGC or time-up-and-go are needed.
- The complexity of GSD II suggests that also combining multiple interventions, such as autophagy modifiers, diet, and exercise, might be an available winning strategy.

demonstrate a slow decline in performance after 24–36 months, likely due to insufficient tissue penetration. To fulfill such unmet needs, therefore, a new enzyme preparation, enriched in mannose was introduced, and its use needs evaluation. 1.2 Diagnostic clues by myopathology.The muscle histopathologic feature of GSDII is the presence of autophagic vacuoles, the degree of vacuolization is extensive in PD on the other hand vacuolar changes are focal, limited in LOPD biopsies, where autophagic vacuoles appear positive with periodic acid Schiff staining and exhibit increased acid phosphatase reaction. When muscle biopsy is morphologically unspecific, because of site choice, the diagnosis might be reached by dried blood spot (DBS), the golden standard is a biochemical enzymatic test in fibroblast cells or muscle [13]. Analysis of variants of the GAA gene is a needed complement [14] to the deficiency of 30–40% GAA enzyme activity. DBS was used in Italy as a valid screening in the LOPED study [15], selecting patients with elevated CK and proximal myopathy. NGS has been used in cases of myopathy cases without a diagnosis [16]. A characteristic morphological change is the internal vacuolar caveolin-3 and dystrophin staining observed in LOPD biopsies [17]. This feature might contribute to the partial ERT response.1.3 ERT Development. Endogenous GAA formation is a multistep process: the 110 kDa precursor enzyme is glycosylated in the Golgi apparatus and acquires mannose-6-phosphate (M6P) residues, is transported to the endoplasmic reticulum, and with successive molecular cleavage, the mature 76/70 kDa alpha-glucosidase enters lysosomes [18]. Cells present specific receptors for the uptake of exogenous lysosomal enzymes: the M6P receptor [19,20]. This allowed new strategies for trials in PD, performed initially with alpha-glucosidase derived from hamster ovary cells [21]. Van der Hout used rabbit milk GAA-derived ERT in PD, exhibiting a homogeneous course [22]. Since PD is rare few studies proved that recombinant human α-glucosidase therapy has been effective in improving cardiomyopathy, the primary cause of death: children death was reduced by 99%, and invasive ventilation by 92%, compared with control [23,24], treated children acquired locomotor function, few were ambulatory [25]. 1.4 Phenotype/Genotype CorrelationThe correlation phenotype/genotype required studies in various subtypes of GSDII. It showed that a combination of two GAA variants, that encode null enzyme activity results in PD. Different variants produce decreased alpha-glucosidase levels in LOPD, the enzyme reduction modifies both the age of onset in patients and course severity. Missense variants and the common IVS1 'leaky' splicing mutation, that originates residual GAA enzyme activity are common in LOPD [26]. De Filippi [27] collected genetic polymorphisms such as ACE, and ACTN3 in a large LOPD series and demonstrated that they influence the age of onset of disease, 6 MWT, and FVC.1.5 Autophagy Role in ERT. Autophagy defect is a major contributor to muscle damage and contributes to muscle atrophy [28]. In GSD II a blocked autophagic flux results in p62 aggregates, vacuolated fibers, and failure of autophagosome turnover, thus impairing cell trafficking and rhGAA uptake. Regarding ERT with neoGAA or other synthetic enzymes, one should consider the role of dysfunctional autophagy, since ERT might lead to lower glycogen in biopsy but does not eliminate p62 aggregates and autophagosome accumulation in muscle fibers. Some experts define Pompe as massive glycogen overload in muscle leading to progressive skeletal muscle damage, and autophagy role [29–32] needs consideration, since a residual autophagic flux contributes to GAA maturation, might protect myofiber from disease progression and improve uptake of recombinant GAA. 1.6 ERT status, an overview of the unmet needs.The first randomized LOTS trial was conducted on a cohort of 90 LOPD patients, that received biweekly intravenous subministration either of recombinant alglucosidase alpha (rhGAA) 20 mg per kg or placebo and the primary outcomes were reached: improvement of distance in 6MWT and % of predicted FVC [33]. The trial suggested that ERT increases muscle strength, as seen from the 6-MWT, while the response of respiratory muscles was limited, suboptimal penetration to muscles provided poor long-standing efficacy. Factors that might influence the body's enzyme distribution are differences in mannose receptor density in skeletal muscles. The open-label extension LOTS trial and numerous observational studies confirmed the stabilization of the disease [34–41]. The translational research investigated pre- and post-ERT muscle biopsies to understand why long-term ERT improves motor performance. The evaluation of glycogen clearance in muscle biopsies pre and post ERT, correlated with reduced glycogen levels after ERT in the EMBASSY study [35] and in the reduction in PAS-staining and vacuolated fibers in muscle biopsies after ERT. Moreover, western blot analysis demonstrated there was the conversion of the 110-kDa precursor to mature 76/70 kDa alpha-glucosidase, implying the enzyme is targeted to lysosomes [40]. This change appeared more marked in less affected muscle fibers, with smaller PAS-positive vacuoles; this might suggest that ERT efficacy is greater when initiated early. However, according to the European guidelines [42] a clinical or instrumental manifestation of GSD II is required to start treatment, while ERT in patients should be stopped in cases of severe infusion-associated reaction (IAR), or loss of efficacy observed for more than 24–36 months [42]. A markedly variable response to ERT was documented in follow-up studies [33–41]. Given the presence of residual GAA, immunogenicity does not explain the variable therapeutic response, and rarely highly neutralizing anti-rhGAA antibody titers have a role in late-onset patients [43,44]. Survival and long-term improvement studies underline the variability of the response [45]. Younger age and initial performance for FVC or

muscle strength were identified as possibly positive prognostic factors, but not confirmed. Since rhGAA biodistribution and cellular uptake might be limited by low sarcolemmal M6P receptor density, therefore, a new enzyme preparation neo-GAA, enriched in mannose, was produced. This review considers the current ERT situation in LOPD, by evaluating the Neo-GAA (Box 1).

2. Characteristics of the new drug

Chemically, avalglucosidase alfa-ngpt or NeoGAA is a preparation, which is by oxime chemistry conjugated with a couple of bis-M6P. NeoGAA is a drug specifically designed for receptor interaction: the bis-M6P of avalglucosidase alfa binds to CI-MPR present in sarcolemma with high affinity, allowing a better drug uptake into muscle fibers. Inside the muscle, NeoGAA acts on lysosomal glycogen degradation by acid glucosidase enzyme activity and since has higher penetration, compared to rhGAA for its chemical structure results in a drug better designed for LOPD. Pharmacodynamics: NeoGAA internalized in muscle fiber enters the sarcoplasm and penetrates lysosomes in active form, where it degrades glycogen [46]. In infused patients, NeoGAA declined monoexponentially 8–12 hours after its intravenous infusion. Pharmacokinetics and metabolism: the distribution volume of NeoGAA was 3.4 L in LOPD with an average half-life of 1.6 h, measured in late-stage cases. Regarding catabolism, we know the NeoGAA clearance is 0.9 L/hour in LOPD. Cost Effectiveness: the analysis is difficult for all orphan diseases including PD and LOPD. Despite substantial survival benefits, alpha-glucosidase appears noticeably less cost-effective because of its high cost. With the evaluation of neo-GAA, no analysis has been presented so far.

3. Phase I-II-III studies

The main purpose of designing neo-GAA was to increase its targeted affinity for the CI-M6P receptor, resulting in a larger tissue penetration [46,47]. Phase 1: the NEO1 Safety study was 6 months long, started in August 2013, and ended in February 2014, and evaluated incremental doses of 5 to 20 mg/kg biweekly in enrolled patients [46]. The efficacy and safety of Nexviazyme were first established in the NEO1 randomized, double-blind, multicenter trial. Phase 2: NEO1 was then followed by a NEO-EXT study with 24 participants 10 naive and 14 switched that ended in February 2020. Nineteen patients entered NEO-EXT (two became pregnant), and the series collected data for 6.5 years. The results of the NEO1 and NEO-EXT trials [47,48] were positive. In NEO-EXT, people with younger age, less than 45 years tended to show better individual improvement than those over 45, suggesting that sarcopenia and muscle wasting affect mobility. Phase 3 COMET Study: a NeoGAA trial comparing it to rhGAA was conducted from February 2016 to February 2021. The 100 patients were administrated either rhGAA or neoGAA biweekly. The primary objective for efficacy was non-inferiority in respiratory function was positive, meeting this aim. COMET trial was performed in 51 Neo-GAA treated and 49 rhGAA treated patients. The respiratory outcome chosen was upright forced vital capacity (FVC) % predicted. Secondary outcomes were 6MWT, QoL, minimal inspiratory capacity, and maximal expiratory pressure. The neoGAA-treated group had a greater improvement in respiratory outcomes and a 2.4% increase in FVC % predicted versus the rhGAA-treated group. It presented an increase in the 6-Minute Walk Test of about 30 m (4.7%). The primary outcome achieved statistical non-inferiority ($p = 0.0074$) [49,50].

Box 1. Drug Summary Box.

Drug Summary: NEXVIADYME is indicated for long-term enzyme replacement therapy (ERT) for treating patients with GSD II or Pompe disease (acid α-glucosidase deficiency). It contains avalglucosidase alfa as the active substance and is given by intravenous infusion.

4. Postmarketing surveillance, pediatric use

Avalglucosidase alfa was approved and surveillance of the neoGAA is underway in LOPD patients with a 40% GAA deficiency. Since the younger patient in the COMET study was 3 years old, patients to be treated should be older than 1 year. Long-term studies regarding embryo-fetal damage or possible carcinogenesis are needed. Children's clinical trials are underway. For similar pathophysiology in Mini-Comet NeoGAA dose in PD patients was established by extrapolation [51]. A preliminary analysis of the mini-COMET study showed a favorable trend for patients treated with a higher dose of Neo GAA (40 mg/kg biweekly) [52], in this context, the range of doses used in the trial appears variable, especially in children, probably since the critical CRIM factor that can be present or absent in pediatric cases and therefore determine a different outcome in relation to his critical presence.

5. Clinical outcomes measures

The choice of clinical outcomes appears critical in the evaluation of the NeoGAA. COMET trial showed a borderline statistical superiority of Nexviazyme over rhGAA ($p = 0.06$). The clinical significance of walking 30 m farther on 6MWT has to be interpreted according to baseline, and it appears more clinically relevant for a late-onset patient with a baseline of 300 m since might indicate the ability to walk a crossroad, than for a patient with a baseline of 500 m. An extension study was performed [50], and the protocol and outcome measures chosen were several. Kishnani in the COMET 3 extension phase offered 100 participants to participate in the extension and 95 were accepted. From the beginning to week 97, the least square mean FVC percentage predicted increased by 2.65 for the NeoGAA-treated group and 0.36 for the switch group. The 6MWT increased by 18.6 m in NeoGAA and 4.6 m in the switch group, indicating that for LOPD cases, it might be worthwhile to start with a new enzyme enriched with mannose-residues to have better motor outcomes. Furthermore, patients who switched to NeoGAA presented disease stability. To evaluate ERT, experts advocate holistic efficacy outcome measures, including coprimary measures alongside FVC and the 6MWT. It is known that 6MWT presents variability

according to fatigue. Additional functional respiratory measurements were used, including minimal expiratory capacity and maximal expiratory pressure. It is noticeable that the scores Gait, Stairs, Chair, and Gower (GSCG) were previously validated in ERT with rhGAA [41] and used in the extension trial. The only reservation in this trial is that the primary endpoint chosen was respiratory, rather than a locomotor one.

6. Safety and tolerability of NeoGAA

Critical IAR was reported in 25% of NeoGAA-treated patients and 33% of patients treated with rhGAA. Adverse Events (AE) or IAR reported on NeoGAA had a more favorable safety profile [45]. The data available on AE are mostly with rhGAA [48–50], treatment-emergent AE was reported in 86% of NeoGAA-treated and 92% of rhGAA-treated patients in the COMET. We still do not fully understand IAR pathophysiology: insights regarding their possible biological mechanisms are given by PD that have <1% residual acid maltase since the presence of CRIM material is important; one-third have no protein. LOPD has residual acid maltase in the 20–30% range. Most LOPD patients carry the IVS1 mutation present in about 90% of Caucasian patients. This common splicing variant produces wild-type GAA protein, in the 10–15% range. The GAA residual protein explains why few IARs are encountered, even if most adults who are rhGAA-treated develop anti-rhGAA antibodies [44]. Their titer level in LOPD correlated with the occurrence and number of IARs according to a 3 years study [53]. Lessard, exploring the French Registry on the use of ERT with rhGAA [54], described a series of 15 cases with AE, nine patients were rechallenged with a modified regimen and a Desensitization Protocol (DP). The other six, not further treated cases, had an unfavorable clinical course. The follow-up showed that four died during the follow-up and one patient was lost to follow-up, between ERT discontinuation and death; unfortunately, after ERT discontinuation, the medical follow-up is often disrupted; both participate in the indirect ERT efficacy. This is addressed by the recommendation that the ERT stop should be short. The proposal to keep ERT stop to less than 6 weeks is coherent with the observation of worsening motor and respiratory function after 2 months of ERT pause during COVID-19. The problem of the restart was examined [54] since there are no established criteria for ERT rechallenge after AE. The question of ERT pursuit/discontinuation was first discussed during collegiate meetings. The benefit/risk ratio was assessed, and the final decision was further discussed with the patient; the risk of pause was explained, as well as the course of the untreated condition, and the impact of ERT pursuit/discontinuation on his/her quality of life.

7. Protocol for AE, ERT rechallenge. Home infusions

The protocol used by Lessard [54] in ERT rechallenge in nine LOPD cases shows that different strategies were adopted. Functional assessment of the patients at ERT discontinuation and its reintroduction to monitor the impact of the transient ERT discontinuation showed that motor and respiratory functions were stable only in the patient that had the shorter ERT interruption (2 months). After 7 months of interruption, the 6MWT decreased and the FVC was stable in a patient. After 16 months, a dramatic deterioration of functional parameters occurred. The patient's decision is difficult when facing a potentially life-threatening pause, compared with a slow progression without a short-term life threat; the final choice is challenging, both for the clinician and the patient, who might refuse ERT reintroduction, balancing the AE experience. Regarding AE management it follows guidelines established by allergy experts. With NeoGAA, some hypersensitivity reactions were reported, but few were considered severe. For those whose main indication is to discontinue the drug immediately, one should cautiously assess DP.

Ditters [55] in a monocentric study compared IAR in patients receiving home versus hospital alglucosidase alpha infusions. IARs occurred in 257 cases: 1.4% of over 18,000 infusions. Most IARs were mild, and 80% of IARs were in the hospital. They therefore suggest that, if the infrastructure allows, home infusion could be implemented for ERT.

8. Pharmacological chaperone therapy (PCT)

One strategy to improve ERT was to use enzyme stabilizers to modulate GAA enzymatic activity, PCT was first experimented with for GSD II, and Pompe-selected variants [56,57]. However, in preliminary trials, no clinical outcome was evaluated [58].

Different doses of the chaperone (50–600 mg) were studied in an open trial, showing a 1.2–2.8-fold increase in GAA activity after PCT [59]. In a phase 3 trial PROPEL combining cipaglucosidase alfa, plus miglustat in 85 cases compared

Table 1. Main clinical trials and outcomes.

Clinical trial	Endpoints primary	Mechanism of action	Key dates
INN Al-glucosidase alfa	6MWT, FVC	Enzyme replacement therapy by intravenous infusion of recombinant human GAA (rhGAA)	First approved on 28 April 2006 (FDA)
Avalglucosidase alfa Sanofi's Phase III COMET trial studying Nexviazyme (NCT02782741)	FVC as primary endpoint; 6MWT included as secondary endpoint	Enzyme replacement therapy An Open-label, Multinational, Multicenter, Intravenous Infusion Study of the Efficacy, Safety,COMET Phase 3	FDA approved August 2021; full trial completion May 2023
Astellas Gene Therapies's Phase I/II FORTIS trial studying AT-845 (NCT04174105)	Safety and pharmacokinetics as primary endpoints; 6MWT and FVC included as secondary endpoints	Gene replacement therapy	Primary completion December 2022
Spark Therapeutics's Phase I/II RESOLUTE trial studying SPK-3006 (NCT04093349)	Safety and pharmacokinetics as primary endpoints; ClinicalTrials.gov no secondary endpoints	Adeno-associated virus gene therapy	Primary completion October 2023
Amicus's Phase III PROPEL trial studying AT-GAA (cipaglucosidase alfa) (NCT03729362)	6MWT as primary endpoint; FVC and GSCG included as secondary endpoints	Chaperone advance enzyme replacement therapy	PDUFA May 2023

favorably to rhGAA plus placebo [60] (Table 1) and resulted in approval for LOPD treatment in the EU [61].

9. Gene therapy trials

There are preliminary gene studies either having 6MWT as the primary outcome, while other trial studies do not foresee efficacy outcome measures. Among the assets in earlier-phase trials, Astellas Gene Therapies' Phase I/II FORTIS trial studying AT-845 has 6MWT and FVC as secondary endpoints, while Spark Therapeutics's Phase I/II RESOLUTE trial studying SPK-3006 does not foresee any efficacy outcome measures (Table 1).

10. Critical issues, open questions

According to experts, the digital health revolution could utilize new equipments such as wearable technologies or gait analysis to monitor outcomes. In diagnosis, the use of artificial intelligence regarding clinical signs is already in progress. Muscle MRI imaging is another useful available tool.

The choice of clinical outcomes appears critical in the evaluation of new drugs such as avalglucosidase alpha, as well as other drugs in trials (Table 1). Experts advocate holistic efficacy outcome measures, including coprimary measures alongside the 6MWT, such as time-up-and-go for postural transition or GSGC, since 6MWT can be highly variable, especially in patients with low mobility.

11. Predictors of response to treatment

Several predictors of prognosis in patients' clinical characteristics such as gender, age, body mass index, genetic background, disease duration, and severity were analyzed. In a study, low body mass index (BMI) was evaluated with the opposite response [62]. While a low BMI might allow better penetration of rhGAA, it appears difficult to reach skeletal muscles in advanced disease. Good clinical conditions and short disease duration seem to be the best predictors of good response to ERT. The response to treatment seems to decline over time. The vacuolization with damage or loss of muscle fibers is an important adverse parameter; however, limited clinical locomotor benefits or stabilization in respiratory function were observed even in advanced cases [63]. Skeletal muscle response or regeneration differs in skeletal muscles with muscle fiber type composition and structure as in limb muscle groups versus diaphragm or respiratory muscles. Muscle fiber types are peculiar in different muscles, and important in determining the response to ERT, type 2 myofibers seem to be less responsive than type I myofibers in GSD II [64].

12. Conclusions

ERT has several limitations and unmet needs, in real-world experience such as limited efficacy over the years, high cost, and hospital administration. NeoGAA appears to hold promise, providing a better exogenous source of GAA for patients, given its preliminary outcome and few AEs, but extended studies with multiple parameters are needed. In particular, motor outcome efficacy studies are needed besides respiratory outcomes, and a clear indication of dosage for adult and pediatric cases is still underway.

13. Expert opinion

NeoGAA trials appear to be a step forward in improving and prolonging over many years the respiratory and motor ERT outcomes, this new enzyme preparation with better delivery to key muscles has demonstrated benefits in both trials and extension [49,50]. NeoGAA is expected to be available shortly, and most patients might accept the switch, as observed in the extension phase. Its use might change the dosage, targeting tissue delivery. Several successful management strategies could be tried: clenbuterol, and albuterol, previously found effective with branched-chain amino acids [65], and other drugs could be tried according to cellular autophagy studies (i.e. rapamycin, metformin, etc.). They should be tried in selected cases after appropriate translational studies since autophagy might exhibit a double face effect in GSD II, i.e both beneficial and detrimental. It is possible to predict in the next 5 years the development of other treatments, such as antisense oligonucleotides or gene therapy. A mandatory field to be explored is the concomitant use of diets and submaximal exercise to improve fatigue in patients. Regular submaximal aerobic exercise and dietary high protein regimen [66] were found to delay disease progression and could be added to ERT [66–68]. In an EPOC meeting, the results of 65 LOPD patients favored ERT efficacy [67] in people undergoing either a concomitant diet or exercise protocol. The bis-MGP of avalglucosidase alpha binds to the cation-independent mannose-6-phosphate receptor which is located on the skeletal muscles. Once the molecule binds to the receptor, the drug enters the cell [68]. In the future, wearable technologies, such as bracelets, smartwatches, and smartphones, will be increasingly used to monitor GSD II patients at home and during sleep. Five years from now neonatal screening for GSD II will be available in several countries, like now in Italy [69], this will change the perspective and policy of ERT in such countries. Accumulation and tissue damage depend on residual enzyme activity and autophagy blockade. Enzyme replacement therapy (ERT) should be started before their symptoms are apparent to achieve optimal outcomes, but it will be difficult to decide how to separate detected infantile from childhood, juvenile, or adult cases. Early initiation of ERT in infantile-onset PD improves survival, reduces the need for ventilation, results in earlier independent walking, and enhances patient quality of life. Newborn screening (NBS) is the optimal approach for early diagnosis and treatment of LOPD, but we need to learn to detect early changes by use of artificial intelligence for symptoms, biomarkers, imaging by muscle MRI, and starting with the newly available enzyme ERT both in childhood and young age so as to prevent irreversible muscle damage. A closer collaboration between metabolic doctors, neurologists, and neuroradiologists is therefore needed and appears to be the next target in this field.

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