POMPE DISEASE: CLINICAL CHARACTERISTICS, DIAGNOSIS, AND MANAGEMENT

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Abstract

Pompe disease is a genetic neuromuscular disorder caused by a deficiency of the acid α-glucosidase enzyme leading to lysosomal glycogen accumulation. Disease phenotypes range from the severe infantile-onset Pompe disease to the slowly progressive late-onset. Until 2006, the management of Pompe disease has been limited to supportive and palliative care. Since 2006, enzyme replacement therapy (ERT) has been available. The requirement of weekly life-long intravenous infusions along with the inability of the enzyme to reach skeletal muscle led to the development of several alternative forms of ERT and the initiation of gene therapy trials in Pompe disease. With the advent of new therapeutic options, a timely diagnosis of Pompe disease is of critical importance, as the prompt therapy has a significant clinical impact on disease course. This article aims to review current literature on Pompe disease and present the latest insights about clinical characteristics, diagnosis, novel therapies, and the impact of COVID-19 pandemic on the management of this treatable neuromuscular disorder.

Key words: Glycogen Storage Disease Type II; Pompe Disease; GAA protein, human; Therapeutics; Review

1. Introduction

Pompe disease (PD) (glycogen storage disease type II, OMIM ID: 232300) is a genetic neuromuscular disorder caused by deficiency of the enzyme acid α-glucosidase (GAA) also known as acid maltase. PD is inherited in an autosomal recessive patternand leads to lysosomal glycogen accumulation [1].

Dr. Joannes Cassianus Pompe, a Dutch pathologist, first described in 1932 an autopsy case of an infant with excessive accumulation of glycogen in her heart muscle, resulting in fatal heart hypertrophy. Dr. Pompe named the disease "cardiomegalia glycogenica" and described the presence of vacuolar storage of glycogen in many organs and tissues, including the myocardium [2]. It was not until 1963 when Dr Henri-Gery Hers recognized that a deficiency in the activity of α-Glucosidase (GAA) was the cause of PD [3] and a few years later, Dr. Andrew G Engel described the same enzyme deficiency in adults presenting with similar clinical manifestations as PD [4].

GAA is a lysosomal enzyme catalyzing alpha 1, 4 and alpha 1, 6 linkages of lysosomal glycogen and hydrolyzing it to glycose [5]. PD is caused by homozygous or compound heterozygous mutations in the GAA gene on chromosome 17q21-23, leading to unstable mRNA producing deficient or null product α-Glucosidase [6]. GAA deficiency causes progressive glycogen lysosomal accumulation, which eventually causes lysosomal rupture and release of the hydrolytic products in myocytes of cardiac, respiratory, skeletal, and smooth muscles [7]. This results in impaired contractile ability and subsequently tissue destruction [8, 9]. Moreover, the accumulation of these substrates in the lysosomes activates several pathogenic mechanisms, including oxidative stress, autophagy, mitochondrial dysfunction, calcium homeostasis and disruption of the mTOR (mammalian target of rapamycin) signaling pathway, contributing altogether to tissue damage seen in PD [10].

The clinical spectrum is variable and ranges from the severe infantile-onset Pompe (IOPD) disease to the slowly progressive late-onset PD (LOPD) [11]. Classic IOPD is characterized by a progressive hypertrophic cardiomegaly and generalized muscle weakness with hypotonia [1]. Without treatment, IOPD progresses to cardiorespiratory failure and death within the first years of life. Patients with LOPD present with a progressive lower limb girdle muscle weakness followed by respiratory symptoms, usually without cardiomyopathy [12]. The phenotypes of the disease are related to the residual enzyme activity. Thus, in IOPD GAA activity is less than 1% of normal, while in LOPD the GAA-activity varies between 1 to 30%. This broad phenotypic spectrum makes the diagnosis challenging.

Table 1. Common clinical features of infantile-onset and late-onse Pompe disease

	Clinical features	Frequency
IOPD	Cardiomegaly/cardiac failure	92%-100%
	Hepatomegaly	90%
	Hypotonia	88%
	Delay or failure in motor development	63-96%
	Respiratory distress	78%
	Hearing loss	75%
	Macroglossia	62%
	Feeding difficulties	53% to 57%
LOPD	Proximal muscle weakness	95%
	Respiratory insufficiency	na
	Exercise intolerance	na
	Gastroesophageal reflux, constipation, diarrhea, vomiting, nausea, and bowel incontinence	na
	Cerebral vasculopathy	67%
	Arterial dolichoectasia of the vertebrobasilar system	52%
	Scoliosis	33%
	Cerebral aneurysms	14%
	Polyneuropathy	na
	Chewing and swallowing difficulties	na

na: not applicable
IOPD: infantile-onset Pompe disease
LOPD: late-onset Pompe disease

PD has an estimated incidence of 1 in 40,000 for all phenotypes in the Caucasian population, while IOPD has a reported frequency of 1 in 138,000 live births [13, 14]. Recently, a novel method based on various registries for GAA variants estimated that PD's incidence was 1 in 23, 232 [15].

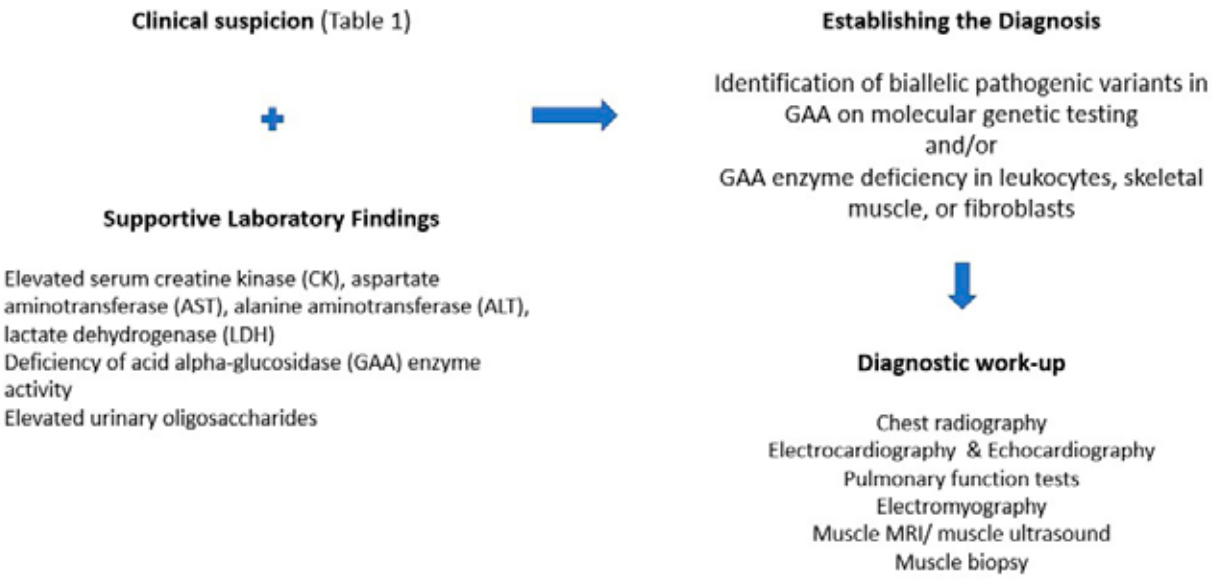
2. Clinical characteristics

PD is classified into infantile-onset (IOPD) and late-onset (LOPD) based on the age at symptom onset and the residual GAA activity. The American College of Medical Genetics (ACMG) Work Group on Management of Pompe Disease in 2006 differentiated the infantile form into "classic infantile" and "non-classic infantile". Classic infantile phenotype includes patients presenting with cardiomyopathy during the first year of life, while non-classic infantile form corresponds to patients with symptom onset at less than 12 months of age, but with mild or no cardiomyopathy and slower disease progression. On the other hand, late-onset form includes childhood or juvenile variant with symptom onset after the 12 months of age and adult-onset with onset of symptoms from adolescence to late adulthood. Typically, these forms do not develop severe cardiomyopathy [16].

Patients with IOPD have a mean age of symptoms onset at two months [17] and their most common presenting symptom is hypotonia [18]{van den Hout, 2003 #42264;Kishnani, 2006 #42270;Marsden, 2005 #42267}. Progressive hypertrophic cardiomyopathy is the key feature of classic IOPD and the median age of death without treatment is six months [1]. Typical signs for infantile onset form include cardiomegaly causing cardiac failure (92%), hypotonia (88%), progressive muscle weakness leading to delay or failure in motor development (63 to 96%), hepatomegaly (90%), macroglossia (62%), poor feeding with subsequent failure to thrive (53% to 57%), respiratory distress (78%), and hearing loss (75%) [1, 17, 19].

Furthermore, brain white-matter abnormalities have been described in adult patients with IOPD that survived after the introduction of enzyme replacement therapy (ERT). IOPD-related white matter lesions

Figure 1. A proposed workflow for the diagnosis of Pompe Disease



seem to follow a characteristic symmetrical pattern, with slow progression over time, affecting the neuropsychological development of these patients in a varying degree [20].

Based on recent data from the Belgian Pompe registry, LOPD patients have a median age of symptoms onset at 28.9 years (range 7 months-68 years) but the diagnosis was reached with a mean delay of 12.9 years [12]. The most common mutation in LOPD patients is c.-32-13 T > G [12, 21] and in contrast to IOPD, patients with this mutation rarely present severe cardiac dysfunction [22].

LOPD patients typically present with proximal muscle weakness, affecting initially the lower limbs and the paraspinal muscles. Progression of the disease is characterized by diaphragm involvement and respiratory distress, and respiratory failure is the most common cause of death in LOPD patients [23]. In a small number of patients (13%), respiratory symptoms may be the presenting manifestation of the disease, while non-invasive ventilation (NIV) is needed in 37% of the patients fifteen years after symptom onset [12]. Macroglossia and hepatomegaly are rarely found.

Nowadays, LOPD is considered as a multi-system disease, affecting in a varying degree not only the musculoskeletal and respiratory system but also the vascular, gastrointestinal, nervous and genitourinary system [24]. According to recent studies, gastrointestinal symptoms may be observed before the diagnosis in 42% of the LOPD patients. The most common manifestation is gastroesophageal reflux, followed by constipation, diarrhea, vomiting, nausea and bowel incontinence [25].

Moreover, involvement of the central nervous system can be found in a significant number of LOPD patients, including the presence of cerebral vasculopathy (67%), arterial dolichoectasia of the vertebrobasilar system (52%), and cerebral aneurysms (14%) [22, 26]. Scoliosis presents in 33% of LOPD patients [27], while polyneuropathy (mainly motor neuronopathy and small fiber neuropathy) has been described as an atypical clinical manifestation [28, 29]. Swallowing disturbances and dysphagia may be also present in LOPD patients, due to bulbar and facial muscles weakness, while ptosis and strabismus may also be rarely observed [30].

The vast clinical spectrum observed in PD, and specifically in LOPD, can be explained by the presence of numerous GAA genotypes caused by the significant number of GAA variants. The last update of the PD GAA variant database described 648 disease-associated variants [24]. Furthermore, the same GAA genotypes may correspond to different phenotypes in LOPD, implicating the impact of secondary modifying genetic factors [8, 20, 31]. On the contrary, a strong genotype-phenotype correlation in IOPD is usually observed [32].

3. Diagnosis

A proposed diagnostic workflow is presented at Figure 1. IOPD should be suspected in any infant with generalized hypotonia and hypertrophic cardiomegaly [33]. Moreover, a history of recurrent respiratory infections or/and liver enlargement is also suggestive of IOPD, although it is not unique to this myopathy. Additional laboratory parameters that should alert physicians towards this diagnosis are the increased levels of creatine kinase (CK), serum glutamic-oxaloacetic transaminase (SGOT), serum

Table 2. Main phenotypic appearance of specific acid α-glucosidase (GAA)

GAA pathogenic variant	Population[1]	GAA enzyme activity	Phenotype
p.Glu176ArgfsTer45 (c.525delT)	Dutch	negligible	severe - predicts IOPD
p.Gly828_Asn882del (c.2482_2646del)	Dutch	negligible	severe - predicts IOPD
c.336-13T>G	na	greatly diminished	LOPD - not associated with IOPD
p.Asp645Glu (c.1935C>A)	Taiwan and China	na	founder effect - IOPD
p.Arg854Ter (c.2560C>T)	African	na	founder effect - IOPD

na: not applicable
IOPD: infantile-onset Pompe disease
LOPD: late-onset Pompe disease

glutamic-pyruvic transaminase (SGPT) and lactate dehydrogenase (LDH). The diagnostic work-up should also include a chest x-ray, an electrocardiogram and a cardiac ultrasound scan, where an enlargement of the cardiac silhouette, a biventricular hypertrophy with short PR intervals and giant QRS complexes and left ventricular noncompaction cardiomyopathy could be observed respectively. The study of glucose tetrasaccharide Glc (4) levels in the urine of infantile-onset patients is a primary diagnostic and therapeutic monitoring biomarker, as it reflects disease progression and correlates with ERT efficacy [34, 35].

Adults with LOPD typically present with progressive muscle weakness, involving proximal lower limbs and paraspinal muscles. The electromyogram (EMG) study demonstrates myopathic discharges, along with numerous myotonic discharges and fibrillations, especially in the paraspinal muscles [36], and although it is not specific, it can strengthen clinical suspicion. Respiratory muscle involvement in adults may occur early in the disease course and it is revealed by the substantially reduced forced vital capacity (FVC) [37]. Additionally, the majority of LOPD patients has elevated CK levels. However, in 5% of these patients CK levels are within the normal range [33]. Screening for the deficiency of acid alpha-glucosidase enzyme (GAA) activity in adults with asymptomatic hyperCKemia has facilitated the early diagnosis of LOPD [38-43].

A confirmed diagnosis of PD, regardless of its form (IOPD or LOPD), warrants confirmatory laboratory testing [44]. The diagnosis is established by the identification of either GAA enzyme deficiency in leukocytes, skeletal muscle, or fibroblasts and/or findings of biallelic pathogenic mutations of the GAA gene on genetic testing [45].

In everyday clinical practice, the preferred method appears to be the measurement of GAA activity. Traditionally, GAA enzyme analysis was performed in skin fibroblasts or muscle biopsy samples. Nowadays, novel methods such as dried blood spot (DBS)-based GAA activity assays are being adopted as a rapid, minimally invasive and reliable first tier test for screening [42, 45]. Of note, a positive DBS test must be subsequently confirmed by a secondary test such as GAA activity assays in tissue samples (whole blood sample, skin, or muscle biopsy) and/or DNA analysis.

With the advent and subsequently decreasing cost of gene sequencing, whole-exome sequencing is being increasingly used in the diagnostic work-up of PD [46]. Gene sequencing offers a high diagnostic yield in patients with suggestive symptoms of PD in whom other differential diagnoses such as muscular dystrophies could not be excluded [47, 48]. In 83 to 93 per cent of patients with impaired or absent GAA enzyme activity GAA sequence analysis may yield two pathogenic variants [49, 50]. Of note, the use of sequence analysis may lead to the detection of benign variants or variants of uncertain significance. If only one or no pathogenic variant is identified, the next step could be gene-targeted deletion/duplication analysis considering that this method may detect deletions or duplications missed by sequence analysis of DNA coding regions [51, 52]. DNA analysis provides genotype-phenotype information as presented at Table 2, is essential for genetic counseling, and facilitates a prenatal diagnosis if the pathogenic mutation is known in the family.

Despite the advances in the field and the increased scientific knowledge about the disease, the confirmation of the diagnosis may still be delayed. According to the worldwide Pompe Registry, the time from symptom onset to initiation of therapy appears to be increased in the year 2008 compared with previous years [53]. Considering that ERT, available since 2006, has been associated with a better disease course in children and adults, it is of paramount importance to diminish diagnostic delay [54, 55].

During the last decade, many countries are implementing newborn screening programs for GAA deficiency, based on several studies in which an early diagnosis followed by an early initiation of therapy was associated with a favorable impact on survival, motor function outcomes and patients' quality of life [56, 57].

4. Management

Until 2006, the management of PD was restricted to supportive and palliative care. During that year, ERT with recombinant human GAA (alglucosidase alfa) administered by intravenous infusions was introduced and substantially changed the natural course of the disease.

The first approved drug therapy (alglucosidase alfa, Myozyme®, Genzyme Corporation) has been available for individuals affected by IOPD disease [58, 59], and another recombinant alglucosidase alfa manufactured at a larger scale (alglucosidase alfa, Lumizyme®, Genzyme Corporation) was subsequently approved for LOPD patients without cardiomyopathy [54]. Alglucosidase alfa is delivered every two weeks as an intravenous infusion at a recommended dosage of 20 mg/kg body weight. In 2014, approval was expanded to patients of all ages irrespective of cardiac involvement, based on the ADVANCE trial, a phase IV, open label study in which patients older than one year of age were included [60].

If left untreated, classic IOPD patients will present an unremitting deterioration, leading to death from cardiac insufficiency during the first two years of life [17]. Infants with non-classic IOPD suffer from less severe cardiomyopathy and may have a prolonged survival based on natural history studies [61]. In untreated patients with LOPD, the estimated survival rate 30 years after the initial diagnosis was 40% [62]. It has become evident that patients with an infantile severe form of the disease benefit the most from ERT, considering that the natural history of the disease and the rate of treatment response varies among individuals with LOPD [54, 63-65].

Apart from ERT, the management of a PD patient of any age should include a multidisciplinary care team consisting of a neurologist or a pediatrician, a geneticist, a physical medicine and rehabilitation physician, a cardiologist, a pulmonologist, an orthopedic, and a nutritionist. Additionally, an international consensus regarding the required outcome measures regularly performed on clinical follow-up and its timeline should be established.

Efficacy of ERT

Several case series and small cohort studies confirmed the short-term and long-term benefits of ERT administration in survival, cardiorespiratory function, and motor development of IOPD patients [59, 66-69]. Prompt initiation of ERT in less severely affected individuals through newborn screening resulted in significant improvement in cardiac, motor and pulmonary function, and survival of these infants [70]. Another prospective study in ten IOPD treated patients diagnosed through newborn screening demonstrated that all patients achieved independent ambulation and none of them required mechanical ventilation after a median treatment duration of 63 months [71]. However, a progressive pelvic girdle muscle weakness was observed in patients older than 2 years old, revealing some limitations of ERT.

The efficacy of ERT in juvenile-onset (2 to 18 years) LOPD patients was recently examined by a systematic review [72]. Based on low quality of evidence, administration of ERT may improve short-term muscle activity and pulmonary function, but no evidence exists about the effect of ERT on survival of these patients. ERT is more effective when administered in younger juvenile-onset patients with a milder disease at baseline assessment.

Between 2006 and 2010, the therapeutic management of LOPD consisted of off-label administration of intravenous ERT with GAA, based on early case-series and case reports [73-76]. In 2010, the first randomized placebo-controlled trial of alglucosidase alfa in 90 LOPD patients revealed a favorable outcome on the 6-minute walk test and stabilization of FVC over 18-months of treatment, and subsequently led to drug approval [54]. Since then, recommendations for managing LOPD patients have been published for many countries [77-81]. In LOPD patients, a duration of ERT up to five years has been proved to improve or stabilize muscle strength, motor and pulmonary function, and survival [64, 82-86]. Several systematic reviews and meta-analyses have been conducted, reporting a significant beneficial effect of ERT in the walking distance achieved by LOPD patients [64, 87]. Recently, a large real-world data study examined the long-term efficacy of alglucosidase alfa in the LOPD population and reported that the initial favourable outcome was followed by a secondary deterioration in multiple outcome measures, highlighting the need for novel therapeutic options [88]. In that context, the European Pompe Consortium (EPOC) developed a specific guidance on starting and stopping ERT in adult patients, taking into consideration the increased costs of a life-long ERT administration [44]. Furthermore, EPOC proposed a minimal set of outcome measures consisting of skeletal muscle strength tests [manual muscle testing (MRC), six minute walk test, timed tests], pulmonary function tests, the fatigue severity scale and patient reported outcomes for monitoring ERT efficacy in PD patients [89]. All patients with PD should perform yearly check-ups at specialized centres by a multidisciplinary neuromuscular team.

Adverse effects of ERT

The most commonly encountered adverse effects (AE) of ERT infusions are severe hypersensitivity and/or infusion reactions [59, 67, 68]. Slowing of the infusion rates and implementation of anaphylaxis pro-

Table 3. Summary of ongoing clinical trials investigating the management of Pompe disease

Interventions	Title	AgesEligible	ClinicalTrialPhase/ Status	Trial Number
Enzymereplacementtherapy				
Alglucosidasealfa	Study to Evaluate Efficacy and Safety in Chinese Patients With Late Onset Pompe Disease With Alglucosidase Alfa Treatment (APOLLO-LOPD)	≥ 3 yearsold	IV/Recruiting	NCT04676373
	Higher Dose of Alglucosidase Alpha for Pompe Disease	upto 60 Years	Observational/ Notyetrecruiting	NCT05017402
	Growth and Development Study of Alglucosidase Alfa	upto 24 Months	IV/Active, notrecruiting	NCT00486889
	A Prospective Study to Observe & Describe Clinical Outcomes of Alglucosidase Alfa Treatment in Patients Upto 6 Months of Age With Infantile-onset Pompe Disease (IOPD)	upto 6 Months	Observational/ Recruiting	NCT04848779
	In Utero Enzyme Replacement Therapy for Lysosomal Storage Diseases (IUERT)	Maternal pregnant women of age 18-50, carrying a male or female fetus at 18 0/7 weeks to 34 6/7 weeks	I/Recruiting	NCT04532047
	PompeLactationSub-Registry	Child, Adult, Older Adult	IV/Recruiting	NCT00566878
Avalglucosidasealfa	A Study to Assess Safety and Efficacy of Avalglucosidase Alfa Administered Every Other Week in Pediatric Patients With Infantile-onset Pompe Disease Previously Treated With Alglucosidase Alfa (Mini-COMET)	6 monthsto 17 yearsold	II/Active, notrecruiting	NCT03019406
	Clinical Study for IOPD Participants Less Than or Equal to 6 Months of Age to Evaluate Efficacy and Safety of Enzyme Replacement Therapy (ERT) With Avalglucosidase Alfa (Baby-COMET)	upto 6 Months	III/Recruiting	NCT04910776
	Avalglucosidase Alfa Extension Study (NEO-EXT)	Child, Adult, Older Adult	II-III/ Active, not recruiting	NCT02032524
AT-GAA [Cipaglucosidase Alfa (ATB200)/ Miglustat (AT2221)]	PROPEL Study - A Study Comparing ATB200/AT2221 With Alglucosidase/ Placebo in Adult Subjects With LOPD	≥ 18 yearsold	III/Completed - No results Posted	NCT03729362
	ZIP Study - A Study of the Safety, Pharmacokinetics, Efficacy, Pharmacodynamics, and Immunogenicity of ATB200/AT2221 in Pediatric Subjects Aged 0 to < 18 Years WithPompe Disease	0-18 yearsold	III/Recruiting	NCT03911505

Table 3. Continuity

Interventions	Title	AgesEligible	ClinicalTrialPhase/ Status	Trial Number
AT-GAA [Cipaglucosidase Alfa (ATB200)/ Miglustat (AT2221)]	Rossella: A Study to Evaluate the Safety, PK, Efficacy, PD and Immunogenicity of Cipaglucosidase Alfa/ Miglustat in IOPD Subjects Aged 0 to <18	0-18 yearsold	III/Recruiting	NCT04808505
	A Study to Assess the Long-term Safety and Efficacy of ATB200/ AT2221 in Adult Subjects With LOPD	≥ 18 yearsold	III/Active, notrecruiting	NCT04138277
Genetherapy				
Recombinant Adeno-Associated Virus Acid Alpha-Glucosidase (rAAV9-DES-hGAA)	Re-administration of Intramuscular AAV9 in Patients With Late-Onset Pompe Disease (AAV9-GAA_IM)	18 to 50 yearsold	I/Active, notrecruiting	NCT02240407
AAV2/8-LSPhGAA	A Phase 1 Study of the Safety of AAV2/8-LSPhGAA in Late-onset Pompe Disease	≥ 18 yearsold	I-II/Recruiting	NCT03533673
SPK-3006	A Gene Transfer Study for Late-Onset Pompe Disease (RESOLUTE)	≥ 18 yearsold	I-II/Recruiting	NCT04093349
AT845	Gene Transfer Study in Patients With Late Onset Pompe Disease (FORTIS)	≥ 18 yearsold	I-II/Recruiting	NCT04174105
Other				
Filgrastim/ Genetically modified autologous bone marrow cell product	Clinical Specimen Collection From-Pompe Disease Patients	3 to 30 yearsold	Observationalstudy/ Recruiting	NCT04476550
NeuRxDiaphragm-pacer (DPS)	Response to Diaphragmatic Pacing in Subjects With Pompe Disease	2 to 65 years old	Observationalstudy/ Recruiting	NCT02354651
Clenbuterol	Phase II Clinical Trial of Clenbuterol in Adult Patients WithPompe Disease	≥ 18 yearsold	II/Notyetrecruiting	NCT04094948

tocols have been applied to avoid these AE. In IOPD, treatment outcome has been negatively affected by cross-reactive immunologic material (CRIM) status. High titers of antibodies against the exogenous GAA have been identified in CRIM-negative IOPD patients, which can lead to clinical deterioration and decreased survival [90]. Individuals with LOPD experience less severe infusion-related AE [91], and AE leading to death have been scarcely reported [92, 93].

Novel therapies in the pipeline

As discussed above, there is an unmet need for a more efficient and cost-effective therapeutic approach for the long-term management of Pompe disease. A summary of ongoing clinical trials investigating novel therapeutic drugs is presented at Table 3.

The requirement for weekly life-long intravenous infusions, along with the inability of the available products to cross the blood-brain barrier, and the fading of ERT efficiency observed over time, led to the development of several gene therapy trials in PD. The first successful phase I/II trial of adeno-associated virus (AAV)-mediated alpha-glucosidase gene therapy in five ventilator-dependent children previously treated with ERT marked a milestone in the management of PD [94]. Gene therapy trials in the pipeline should focus on the safety profile and the long-term therapeutic effect on pulmonary and motor function.

Another drawback of the currently used ERT is the inability of the enzyme to reach skeletal muscle, due to the limited number of mannose-6-phosphate (M6P) groups on alglucosidase alfa and the decreased expression of the cation-independent mannose 6-phosphate receptor (CI-M6PR) on the surface of

muscle cells [95, 96]. Hence, alternative forms of ERT with an increased affinity for this receptor are being developed. Avalglucosidase alfa (Nexviazyme®, Sanofi Genzyme) is a second generation recombinant human GAA enzyme which recently received an approval by the U.S. Food and Drug Administration (FDA) for the treatment of LOPD patients older than one year of age [97]. In a phase III trial, treatment-naive patients with LOPD who received avalglucosidase alfa demonstrated a greater improvement in pulmonary and motor function outcomes compared with alglucosidase alfa treated individuals [98]. The European Medicines Agency's (EMA) final recommendation is expected.

In another effort to enhance the efficiency of ERT, a combination of alglucosidase alfa with clenbuterol was studied in a phase I/II trial, demonstrating a positive safety profile along with motor function improvement [99]. Additionally, AT-GAA (Amicus Therapeutics, USA) is a novel ERT combining recombinant human GAA with a pharmacological chaperone that is evaluated in PD patients of any age.

Finally, aerobic exercise along with a low carbohydrate - high protein diet have been studied as adjunctive therapies to ERT [100, 101], while another ongoing trial examines diaphragmatic pacing as a rehabilitative tool to minimize mechanical ventilation requirements based on a previous case series presenting positive results [102].

Impact of COVID-19 pandemic on Pompe disease management

As of September 7 2021, the COVID-19 pandemic has affected more than 220 million individuals with over 4.5 million deaths worldwide [103]. Despite the abundant scientific data rapidly published about the clinical syndrome caused by COVID-19 and the rapid development of effective vaccines, humanity is still fighting to control virus spread almost two years after COVID-19 outbreak [104]. COVID-19 associated restrictions and the recurrent so-called lockdowns have negatively impacted economic and healthcare systems worldwide.

Patients with chronic neuromuscular diseases such as PD had restricted access to the hospitals due to the increased risk of contamination during the first year of the pandemic. According to the French Rare Health Care for Neuromuscular Diseases Network (FILNEMUS) guidelines, in-hospital ERT infusions had to be postponed over a period of 1 to 3 months and home infusions were suggested [105]. Indeed, the transition to home-therapy seemed to be the most effective access to ERT during pandemic and was implemented in many countries around the world [106, 107]. However, in a recent German study, interruption of ERT in LOPD patients for a mean time of 49.42 days (SD ± 12.54) was associated with a significant deterioration in pulmonary and motor function tests and other objective outcome measures [108]. Hence, in order to provide PD patients with the best medical care and access to the hospitals, physicians should encourage all patients who are not taking immunosuppressive agents to receive COVID-19 vaccines, as suggested by American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) [109].

5. Conclusions

Even though PD was a neuromuscular disorder associated with a very poor prognosis, the approval of ERT in 2006 has substantially changed the natural course of the disease, and mainly the severe form of IOPD. Nevertheless, an unmet need for a more efficient therapeutic approach for the long-term management of these patients remains until today. With the advent of alternative forms of ERT and gene therapy applied in PD, the timely diagnosis is still of a critical importance, as the earliest initiation of the therapy has a significant clinical impact on disease course.

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