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REVIEW

Management of Pompe disease alongside and beyond ERT: a narrative review

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Background. Pompe disease is a lysosomal storage disorder that primarily affects muscles, and its natural history has been transformed over the past 20 years by therapies designed to restore the deficient enzyme function, from the first enzyme replacement therapies (ERTs) to the gene therapy currently in development. However, despite these ground-breaking innovations, the importance of a multi-system and rehabilitative approach remains critical, as it addresses the complex systems involved in the disease and optimizes the success of pharmacological treatments.
Methods. We conducted a narrative review of the current pharmacological treatments approved for Pompe disease, as well as those undergoing clinical trials. We also reviewed international recommendations for managing respiratory, musculoskeletal, and cardiac function specially focusing on the late-onset form.
Results. There are no universally agreed guidelines for the multidisciplinary management and many recommendations are based on expert consensus and small interventional studies. Nevertheless, combined approaches involving ERT therapy along with specific rehabilitation and nutritional programs appear to yield beneficial effects.
Conclusions. Pompe disease, one of the first neuromuscular diseases to benefit from the approval of disease-modifying therapies, is a paradigm for the importance of an integrated therapeutic-rehabilitative approach.

Key words: late-onset Pompe disease, LOPD, glycogenosis, enzyme-replacement therapy, ERT, gene therapy

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Introduction

Pompe disease, also known as Glycogen Storage Disease type II, is a rare autosomal recessive metabolic disorder caused by mutations in the GAA gene, leading to the loss of all or part of the enzyme acid alpha-glucosidase (GAA) [1]. This enzyme is responsible for breaking down glycogen in the lysosomes, making it available as glucose for energy production [2]. Depending on the residual activity of the enzyme, there are two main phenotypes of the disease, which differ in the age of onset and the systems affected: the severe infantile-onset form (IOPD), which begins within the first year of life and is characterized by early cardiomyopathy and muscle weakness, and the late-onset form (LOPD), which encompasses childhood, juvenile, and adult forms, primarily affecting the skeletal axial,

limb-girdle, and respiratory muscles, leading to progressive motor impairment and respiratory insufficiency.
Over the years, wider systemic involvement has been recognized in LOPD, with evidence of glycogen accumulation in various tissues, explaining vascular abnormalities (such as basilar artery aneurysm and dilation of the ascending aorta), nervous system, oro-gastrointestinal, urinary tract and bone abnormalities, and white matter changes on MRI [3,4].
Given the complexity of the disease, a multidisciplinary approach is essential for optimal management, involving a team of specialists, including neurologists, cardiologists, pulmonologists, physiotherapists, psychologists, and dietitians, to provide comprehensive care. Enzyme replacement therapy (ERT) is the primary treatment but must be complemented by supportive therapies such as physical rehabilitation, respiratory support, and nutritional advice to ensure coordinated interventions and improve quality of life [5].
The aim of this narrative review is to compile all existing evidence on the multidisciplinary management of patients with Pompe disease, specifically focusing on LOPD, from disease-modifying therapies to rehabilitation, in order to provide clinicians with practical and up-to-date guidance in light of the evolving treatment landscape.

Disease-modifying pharmacological approaches

Enzyme Replacement Therapy (ERT)

Three ERTs are currently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of Pompe disease (Tab. I).
Traditionally, ERT has been administered in a clinical setting, requiring patients to visit hospitals or infusion centers for intravenous infusions on a bi-weekly basis. Noteworthy, home infusion of ERT has become an increasingly important option for managing Pompe disease, offering patients greater flexibility and comfort in their treatment regimens. To ensure safety, patients and caregivers should be thoroughly trained in the proper techniques for administering infusions, managing potential side effects, and monitoring adverse reactions. To date, home infusion has been shown to be as safe and effective as clinic-based infusions, provided that appropriate medical oversight is maintained, and it is particularly beneficial for patients living in remote areas or those with mobility challenges [6].
Furthermore, it can reduce healthcare costs by minimizing hospital visits and facilitating long-term adherence to treatment.
A recent update to the 2017 European Pompe Consortium (EPOC) recommendations suggested criteria for starting ERT (the patient should have a confirmed diagnosis of Pompe disease, be clinically symptomatic or have supportive paraclinical signs, have residual skeletal and respiratory muscle function that is functionally relevant, and should not have another life-threatening illness), switching from one therapy to another (in case of worsening skeletal muscle and/or respiratory function during a minimum standard ERT treatment period of 12 months or in case of severe infusion-associated reactions), or discontinuing therapy (in case of worsening skeletal muscle and/or respiratory function during the first 2 years after starting or switching treatment, infusion-associated reactions with all types of ERT, or high neutralizing antidrug antibody titers) in LOPD patients [7].
However, more scientific evidence is needed to determine the real benefits of switching therapies and which enzyme treatment is preferable on a patient-by-patient basis.

Alglucosidase alpha

The first marketed ERT for both infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD) was alglucosidase alpha (Lumizyme in the US, Myozyme in the EU), approved in 2006. In IOPD patients with early symptom onset (within 6 months of age), alglucosidase alpha was found to increase both overall survival and ventilation-free survival, compared to controls from historical cohorts. It also showed a positive effect on cardiac involvement, with a reduction in left ventricular mass, on motor function, with the achievement of walking or sitting ability, and on the increase in growth parameters [8].
A second study also confirmed the safety and efficacy of the treatment in IOPD patients aged 6 months to 3.5 years [9]. Nevertheless, clinical deterioration in ventilation, feeding, and motor function occurs after an average follow-up of 6 years [10]. In LOPD, a randomized, double-blind, placebo-controlled trial in 90 naïve patients (aged 10 to 70 years) validated the use of alglucosidase alpha in this population [11]. Treated patients showed an increase in the 6-minute walk test (6MWT) distance (+15.0 meters versus -7.5 meters in the placebo group) ($p = 0.0283$) and stabilization of the lung function (median change in forced vital capacity [FVC] of 0.0% versus -3.0% in the placebo group) ($p = 0.0026$) at 78 weeks. The improvement in walking distance and stabilization of lung function were maintained at 104 weeks in the open-label extension phase [12]. The efficacy of alglucosidase alpha has also been demonstrated at the histopathological level, with evidence of glycogen clearance from the lysosomal compartment (but not from the cytoplasmic compartment, where glycogen blebs accumulate after lysosomal rupture in more advanced stages) in both pediatric and adult patients [13-15]. Subsequent real-world experience has replicated these results, as shown in four studies (two Dutch, one German, and one Italian) conducted on a pooled sample of 283 patients, with follow-up ranging from 2 to 5 years [16-19]. In addition, it has been shown that the peak of response in terms of motor outcome occurs in the first 2-3 years of therapy, which is more pronounced in patients with shorter-lasting disease, and that the goal of stabilization can be achieved even in advanced disease with severe respiratory failure [16,17,20,21].
Some shortcomings of the treatment need to be considered. Firstly, in IOPD patients with complete absence of the native enzyme due to deleterious GAA mutations, hereafter referred to as "cross-reactive immunogenic material (CRIM)-negative," high-titer neutralizing antibodies against recombinant human GAA (rh-GAA) lead to inactivation of the exogenous enzyme and ineffectiveness of the treatment, resulting in reduced overall survival and poorer clinical outcomes [9]. In this population, immunomodulatory therapy, including a combinatorial approach aimed at interrupting B- and T-cell responses, is recommended and should be started as early as possible to achieve complete elimination of anti-rhGAA [22,23]. There is also evidence of immunogenicity against the enzyme in adult LOPD patients, but in most cases, a low to intermediate titer of non-neutralizing antibodies does not appear to affect treatment efficacy [11,24,25]. However, a pre-

Table I. Approved treatments for Pompe disease and registration trials.

	Study population and sample	Study design	Endpoints/outcome measures	Main results	Trials
Alglucosidase Alpha	IOPD n=18, <6 months (vs n=42 controls from historical cohort)	20mg/kg qow or 40mg/kg qow [for 52 weeks] (n=16 in OLE up to 150 weeks)	Primary: safety and efficacy → survival and ventilation-free survival at 1 year of age Secondary: PK, PD Primary: long-term safety and efficacy	W52: n=18/18 survived (HR 0.05, p< 0.001) n=15/18 ventilation-free n=14/14 decrease of LVM, n=3/14 normalization of LVM W104: n=16/16 survived n=10/16 ventilation-free n=5/8 normalization of LVM	AGLU01602 NCT00059280 (PHASE 2/3) AGLU02403 NCT00125879 (PHASE 2/3)
	IOPD n=21, 6-36 months	20mg/kg qow (and 40mg/kg qow after 26 weeks for n=8) [for 52 weeks]	Primary: safety and efficacy → survival Secondary: PK, PD	W52: n=16/21 survived (HR 0.301, p=0.0166) n=16/16 decrease of LVM, n=6/12 normalization of LVM W104: n=14/21 survived n=7/21 ventilation-free (versus n=16/21 at baseline) n=9/10 normalization of LVM	AGLU01702 [NCT00053573] (PHASE 1/2)
	LOPD n=90, >8 yrs, ambulatory, ventilation-free	20mg/kg qow or placebo (2:1 ratio) [for 78 weeks] 20mg/kg qow (OLE)	Primary: 6MWD and FVC Secondary: QMT, MIP, MEP, MOS SF-36 Primary: safety (until 2.5 years), 6MWD, FVC Secondary: QMT, MIP, MEP, MOS SF-36	W78: 6MWD: +25.13 m (mean) in treated vs -2.99 m (mean) in placebo groups (p=0.03) FVC: +1.20% (mean) in treated vs -2.20% (mean) in placebo group (p=0.006) W104: 6MWD: +21.3 m (mean; compared to LOTS bsl) and -6.9 m (mean; compared to OLE bsl) FVC: +0.8% (mean; compared to LOTS bsl) and -0.7% (mean; compared to OLE bsl)	"LOTS" AGLU02704 [NCT00158600] (PHASE 3) AGLU03206 [NCT00455195] (PHASE 4)
Avalglucosidase Alpha	LOPD n=24, ≥18 yrs (10 naïve and 14 previously treated with alglu for at least 9 months)	5, 10, or 20mg/kg qow for both groups [for 27 weeks]	Primary: skeletal muscle glycogen content by MRI and biopsy, urinary Hex4 Exploratory: FVC, FEV1, MIP, MEP, PEF, 6MWD, GSGC, GMFM-88, QMFT, HHD, PedsQL	- Muscle glycogen levels unchanged from baseline to W25 in both groups - Hex4 decreased at all doses except for 5mg/kg at W13 for the switch group - Pulmonary function was stable or improved at W25 in both groups - 6MWD was stable or tended to increase in both groups	"NEO1" TDR12857 [NCT01898364] (PHASE 1)
	n=19 from NEO1	5, 10, or 20mg/kg qow [for 104–156 weeks], then 20mg/kg qow for all [up to 6.5 years]	Primary: long-term safety, PK Secondary: PD (skeletal muscle MRI and biopsy, urinary Hex4) and prespecified exploratory efficacy variables (serum CK, AST, ALT; 6MWT; FVC, MIP, MEP)	- FVC % and 6MWD were mantained up to 6.5 years of follow-up - Tendency to improvement of elevated baseline Hex4 and CK over time	"NEO-EXT" LTS13769 [NCT02032524] (PHASE 2)
	LOPD n=100, ≥16 yrs → avalglu (n=51) → alglu (n=49)	20mg/kg qow for both groups [for 49 weeks]	Primary: FVC Secondary: 6MWD	- FVC: Δ 2.43% between groups (+2.89% in avalglu, +0.46% in alglu) p=0.074, non-inferiority test - 6MWT: Δ 30.01 m between groups (+32.21 m in avalglu, + 2.19 m in alglu) (p=0.040)	"COMET" EFC14028 [NCT02782741] (PHASE 3)
	IOPD n=22, <18 yrs, previously treated with alglu and showing: → clinical decline (cohort 1 and 2) or → suboptimal response (cohort 3)	C1→ avalglu 20mg/kg qow C2→ avalglu 40mg/kg qow C3 (1:1)→ avalglu 40 mg/kg qow or alglu (current dose) [for 6 months]	Primary: safety Secondary: GMFM-88, GMFCS-E&R, QMFT, Pompe-PEDI, LVMI and LVM, presence/absence of ptosis, serum CK, urinary Hex4, 6MWD, respiratory function	6MWD, GMFM-88, QMFT, Pompe-PEDI, ptosis, and LVM improved or stabilized at avalglu 40mg/kg qow, whereas stabilized or declined in avalglu 20mg/kg qow or alglu	"MINI-COMET" ACT14132 [NCT03019406] (PHASE 2)
	IOPD <1 yrs, treatment- naïve, ventilation-free	avalglu 40mg/kg qow [for 52 weeks]	Primary: safety and efficacy → survival and ventilation-free survival Secondary: LVM, AIMS, body length and weight, urinary Hex4	No unexpected safety issues at data cut-off (presented at 20th annual WORLDSymposium) (no published data yet)	"Baby-COMET" EFC14462 [NCT04910776] (PHASE 2)

Table I. Follows from the prevous page.

	Study population and sample	Study design	Endpoints/outcome measures	Main results	Trials
Cipaglucosidase Alpha + Miglustat	LOPD 18-75 yrs C1: n=1 ERT(2-6y)-switched amb C2: n=6 ERT(>2y)-switched non-amb C3: n=5 ERT-naïve amb C4: n=6 ERT(>7y)-switched amb	Stage 1: ascending dose of cipaglu (5>10>20mg/kg qow) [for 6 weeks] Stage 2: cipaglu 20mg/kg qow + miglustat 120>260mg [for 12 weeks] Stage 3: cipaglu 20mg/kg qow + miglustat 260mg [2 years, ongoing] [for 18 weeks + LTE]	Primary: 6MWD Secondary: TUG, GSGC, MMT, R-PAct, Rotterdam Handicap, Fatigue Severity Scale	n=8/9 (88.9%) of ERT-experienced and n=4/4 (100%) of ERT-naïve patients experienced an improvement in 6MWD at month 48 FVC improved (Δ>3%) in 66.7% of ERT-experienced and 75% of ERT-naïve patients at month 48	ATB200-02 [NCT02675465] (PHASE 1/2)
	LOPD n=125, ≥18 yrs Naïve or previously treated with alglu (2:1) → cipaglu + miglustat (n= 85) or → alglu + oral placebo (n= 40) n=118 (n=81 from cipaglu + miglustat and n=37 from alglu + oral placebo)	Cipaglu 20mg/kg + miglustat qow or alglu 20mg/kg + oral placebo qow [for 52 weeks] OLE [for 4 years, ongoing]	Primary: 6MWD Secondary: FVC, MMT, PROMIS, GSGC, time to complete GSGC component tests and TUG, MIP, MEP, SNIP, SLC, MVC, SGI, PGI, R-PAct, EQ-5D-5L, serum CK, urinary Hex4 Primary: safety Secondary: 6MWD, FVC, R-PAct, EQ-5D-5L, PROMIS, GSGC, PGI, serum CK, urinary Hex4, anti-drug antibodies	6MWD: Δ 13.6 m between groups (+20.8 m in cipaglu+miglustat, +7.2 m in alglu+oral placebo) (p=0.071) FVC: Δ 3.0% between groups (-0.9% in cipaglu+miglustat, -4.0% in alglu+oral placebo) (p=0.023) Similar incidence of TEATs between groups W104: Overall maintained improvements (6MWD, biomarkers) or stabilization (FVC) from baseline	"PROPEL" ATB200-03 [NCT03729362] (PHASE 3) ATB200-07 [NCT04138277] (PHASE 3)
	IOPD C1: 6 months-18 yrs, ambulatory, ERT-treated for at least 6 months C2: < 6 months, ERT-naïve	Cipaglu 20mg/kg + miglustat qow [for 104 weeks]	Primary: safety	(ongoing)	"ROSSELLA" ATB200-08 [NCT04808505] (PHASE 3)

Abbreviations: AIMS; Alberta infant motor scale; alglu, alglucosidase alpha; amb, ambulatory; avalglu, avalglucosidase alpha; bsl, baseline; EQ-5D-5L, 5-level EQ-5D version; FEV1, forced expiratory volume in 1 s; GMFCS-E&R, Gross Motor Function Classification System-Expanded and Revised; GMFM-88, Gross Motor Function Measure-88; GSGC, Gait, Stair, Gowers' Maneuver, Chair; HHD, hand-held dynamometry; Hex4, glucose tetrasaccharide; IOPD, infantile onset Pompe disease; LOPD, late onset Pompe disease; LTE, long-term extension; LVM, left ventricular mass; LVMI, left ventricular mass index; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MMT, manual muscle test; MOS SF-36, Medical Outcomes Study Short Form-36; MRI, magnetic resonance imaging; MVC, maximum vital capacity; OLE, open-label extension; PD, pharmacodynamic; PedsQL, pediatric quality of life inventory multidimensional fatigue scale – adult report; PEF, peak expiratory flow; PGI, physician's global impression of change; PK, pharmacokinetics; Pompe-PEDI, Pompe pediatric evaluation of disability inventory; PROMIS, patient-reported outcomes measurement information system; QMFT, Quick Motor Function Test; QMT, quantitative muscle testing; qow, every other week; R-PAct, Rasch-built Pompe-specific activity; SGI, subject's global impression of change; SNIP, sniff nasal inspiratory pressure; SVC, slow vital capacity; TEAE, treatment emergent adverse events; TUG, timed up-and-go test; yrs, years of age; 6MWD, distance walked in 6-min walk test; Δ, difference.

vious study from our group showed improvement in MRC values in negative-antibody patients compared with positive-antibody patients at follow-up in the first 36 months of treatment, and some isolated anecdotal cases of adult patients developing high IgG antibody titers (up to 1:800,000) during the first year of treatment with ERT, leading to deterioration in pulmonary and motor function, have been reported [18,25-27].

Secondly, the efficacy of ERT with alglucosidase alpha usually declines invariably after the first 3 to 5 years of treatment, and the reason for this phenomenon is still unknown [28]. Some hypotheses for this loss of efficacy include (i) the variable number of bis-mannose 6-phosphate (M6P)/insulin-like growth factor II receptors expressed on the muscle surface, which are necessary for the uptake and endocytosis of the enzyme; (ii) the overloading of the autophagic system, which is no longer able to dispose of cytoplasmic glycogen accumulations; and (iii) the limited access and function of the activated enzyme at the level of glycogen stores [28].

Avalglucosidase alpha

The second-generation ERT (neoGAA), avalglucosidase alpha (Nexviazyme in the US, Nexviadyme in the EU), was designed to overcome the limited uptake of the molecule by muscle fibers by providing it with additional mannose-6-phosphate (M6P) groups compared to the original product, thereby increasing its binding affinity to the cation-independent M6P receptor (CI-MPR). Initial studies of this new compound in mouse models in 2009 showed a fivefold increase in lysosomal glycogen clearance in muscle compared to the original rhGAA [29]. The safety, pharmacokinetic, and pharmacodynamic profiles of avalglucosidase alpha were first investigated in an open-label phase 1 study and confirmed at six years of follow-up in the extension study [30,31]. Its clinical efficacy in terms of respiratory function and ambulation in patients with LOPD was evaluated in a randomized, head-to-head phase 3 trial, which demonstrated non-inferiority to alglucosidase alpha [32]. Another study specifically designed for IOPD patients aimed to evaluate ascending doses of treatment in a popula-

tion previously treated with alglucosidase alpha and showing clinical decline or suboptimal response; the results highlighted clinical stabilization or improvement at the maximum dose studied (40 mg/kg every other week) and stabilization or decline at the lower dose (20 mg/kg every other week) and at the standard dose of alglucosidase alpha (20 mg/kg every other week) [33]. A study in naïve IOPD patients is ongoing [NCT04910776]. These results led to the US FDA's approval of avalglucosidase alpha for the treatment of patients aged 1 year and older with LOPD.

ERT Plus Chaperone Therapy

Another therapeutic approach being investigated since the early 2000s is the combinatorial treatment of ERT with chaperones, which are small molecules able to stabilize the infused enzyme by promoting the correct conformation of the misfolded protein. Preclinical studies in patient-derived fibroblasts and animal models demonstrated increased lysosomal trafficking, maturation, and intracellular enzyme activity following administration of N-butyldeoxynojirimycin (NB-DNJ), one of the most studied chaperone molecules, alone or in combination with rhGAA [34-37]. The new combination therapy was tested for the first time in Pompe disease in a 13-patient study, in which efficacy was assessed by measuring GAA activity by tandem mass spectrometry in dried blood spots. Increased activity (greater than 1.85-fold) was demonstrated in 11 out of 13 patients and persisted in the entire cohort at 36 hours from administration, with a peak at 24 hours [38]. The trial that led to the third drug approval was PROPEL, which compared the safety and efficacy of cipaglucosidase alpha (a next-generation rhGAA with optimized glycosylation and high levels of M6P) in combination with the chaperone miglustat to standard treatment (alglucosidase alpha) plus oral placebo [39]. The study did not demonstrate statistical superiority for the primary endpoint (change in 6MW distance from baseline to week 52), but did demonstrate statistical superiority for the secondary endpoint (change in predicted FVC%) ($p = 0.023$). Based on these successes, it was approved for the treatment of LOPD patients by the European Commission on March 27, 2023; results from the ongoing open-label extension study will clarify the long-term effects of cipaglucosidase alpha + miglustat in this patient population.

Gene Therapy

In recent years, gene therapy has been explored for several rare genetic diseases, aiming to introduce the defective or missing gene into the body to restore a functional protein and ameliorate or correct the disease phenotype. Preclinical studies have also been conducted in Pompe disease, investigating both adeno-associated viral (AAV) gene therapy for in vivo applications and lentiviral (LV) gene therapy for ex vivo applications. The general mechanism involves recognition and endocytosis of viral capsids by glycosylated receptors on the cell surface, low nuclear integration and persistence of the delivered DNA molecules in the host genome as extrachromosomal, double-stranded circular episomes, and transcription [40]. Each AAV serotype has specific tissue tropism that enhances delivery to target cells [41].

The first experiments with AAV-GAA in Pompe disease were based on direct delivery of the transgene into the skeletal muscle of mice, resulting in a reduction in glycogen content and high levels of GAA expression "locally," but without similar results in the "distant" muscle mass. Association with a muscle-specific creatine kinase (MCK) promoter resulted in effective delivery even in immunocompetent mice, inducing a humoral immune response but avoiding a cellular one (as witnessed by muscular CD4+/CD8+ lymphocyte infiltrates, as seen in the absence of a specific promoter) [42]. Nevertheless, it was clear from the outset that late correction of GAA expression in more compromised mice was not effective in restoring strength, despite the pathological resolution of glycogen storage in muscle [43]. These partial results led to the investigation of the intravenous route of administration. Systemic administration of AAV8-MCK-hGAA (AT845) in mice resulted in a dose-dependent increase in GAA activity, glycogen clearance in muscle and heart, and functional improvement; this study also highlighted the importance of considering the toxicity of AAV vectors encoding human proteins when testing in non-human species, as a xenogeneic immune response was observed in macaques transfected with human GAA [44]. A newly developed AAV vector, thanks to a specific promoter (cytomegalovirus enhancer-chicken β-actin), was able to successfully transduce CNS, skeletal, and cardiac muscles [45]. A therapeutic approach combining a liver-targeted AAV serotype with a liver-specific promoter resulted in greater and more sustained GAA expression in vivo, paving the way for the concept of the "liver depot," i.e., high liver expression of GAA accompanied by secretion into the bloodstream and receptor-mediated uptake into the target tissues (heart and skeletal muscles) [3,46,47]. Efficacy is achieved by evading humoral and cellular immunity through the activation of Tregs, a phenomenon exclusive to the sinusoidal endothelial cells of the liver, leading to immune tolerance [47,48]. It is also of fundamental importance from the perspective of ERT, representing a potential immunomodulatory, tolerogenic (low-dose gene) therapy for CRIM-negative subjects [49,50]. In addition, co-expression of secretable GAA in both liver and neurons using a tandem liver-neuron promoter (LiNeuP) has been shown to simultaneously improve muscle strength and respiratory defects in both newborn and already deficient mice [51,52].

The intrathecal and intracerebroventricular routes of AAV-GAA delivery have also been studied in mouse models, with positive results in terms of neuromuscular improvement and correction of hypertrophic cardiomyopathy, ventilatory function, and motor coordination [53-55].

An important consideration in the human context is the evidence from preclinical studies that, at the same liver-targeted AAV-GAA dose normalized for body weight, newborn mice have lower tissue glycogen clearance due to a rapid loss of vector genomes during growth [56]. Children with Pompe disease will therefore require higher doses of the vector.

To date, a phase I/II trial on the intra-diaphragmatic delivery of gene therapy in children with chronic, full-time mechanical ventilation showed safety and modest improvements in some measures of ventilatory performance (notably not maximal inspiratory pressure, MIP) after 180 days [57,58]. More recently, the first phase I study on the intravenous administration of an AAV8-GAA targeting the liver in 3 LOPD patients [NCT03533673] [59] showed a significant increase in serum GAA activity at 52 weeks, allowing discontinuation of ERT after 26 weeks due to clinical stabilization. Patients were treated with immunoprophylaxis (prednisone 60 mg/day for one month) and did not develop any anti-capsid T-cell responses. There were no treat-

ment-related serious adverse events.
Transplantation of ex vivo genetically modified hematopoietic stem cells (HSCs) transduced with a lentivirus (LV) vector expressing human GAA has been shown to be efficient and tolerogenic. So far, only preclinical studies have investigated this therapeutic approach. The first one showed low but detectable GAA enzyme activity in peripheral blood and bone marrow cells at 17 weeks post-infusion, significant glycogen reduction in gastrocnemius tissue (but not in the heart), and the absence of a subsequent immune response to a 5-week protocol of ERT [60]. Another study showed persistence of GAA enzyme activity for up to 18 months after transplantation and significant glycogen clearance in the heart, diaphragm, spleen, and liver of mice, with reversal of cardiac remodeling and improvement in respiratory function, skeletal muscle strength, and motor performance [61]. In a more recent paper, the use of a codon-optimized GAA (GAAco) induced almost complete normalization of glycogen in the heart, muscle, and brain, with evidence for the presence of the enzyme in a large proportion of microglia and in all astrocytes [62].

Alternative-target therapies

In recent years, alternative therapeutic approaches have been developed that target other mechanisms involved in the pathogenesis of the disease. These include oxidative stress resulting from autophagic dysfunction, which has been shown to hinder the ability of rhGAA to restore GAA activity in cells, likely by affecting the trafficking of vesicles and membrane-associated proteins (such as M6PR) [63]. A recent study showed that the use of some antioxidants (N-acetylcysteine and idebenone, in particular) co-administered with rhGAA improved M6PR localization at the plasma membrane of Pompe disease fibroblasts and enhanced GAA processing and activity in both in vitro and in vivo models (the latter at the level of the diaphragm, quadriceps, and liver) [63].
Since the most common variant, c.-32-13T > G (IVS1), leads to partial or complete skipping of GAA exon 2, another approach being explored is to inhibit the splicing regulatory element of this region using a small nuclear RNA (snRNA)-based antisense oligonucleotide (AON) to promote the inclusion of exon 2 and thus restore canonical GAA splicing [64]. The efficacy of this approach was also demonstrated in multinucleated myotubes derived from induced pluripotent stem cell (iPSC)-myogenic progenitors [65], in addition to patient-derived fibroblasts [64,66].
Substrate reduction therapy has also been investigated. This is achieved by inhibiting the muscle-specific enzyme glycogen synthase 1 (GYS1) using a phosphorodiamidate morpholino oligonucleotide (PMO) designed to induce exon skipping and a premature stop codon [67]. Positive results were recently reported from a Phase 1 study involving 112 healthy volunteers, demonstrating the safety and ability of MZE001, a GYS1 inhibitor, to reduce glycogen accumulation in peripheral blood mononuclear cells (PBMCs) [NCT05249621] (unpublished data) [68].

Respiratory function management and rehabilitation

Respiratory involvement is a common complication in LOPD, affecting up to 75% of patients due to weakness in the axial, intercostal, abdominal, and diaphragm muscles. This may also be one of the presenting symptoms of the disease before strength deficits are noticeable [69-71]. Historical data on the decline of forced vital capacity (FVC) over time show a loss of -1% to -4.6% per year [17,72]. Among the pulmonary manifestations, restrictive ventilation and ineffective cough are key to assess both at baseline and when clinically suspected. This can be done using pulmonary function tests, including upright and supine FVC, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), sniff nasal inspiratory pressure (SNIP), peak cough flow (PCF), blood gas analysis, and transcutaneous monitoring of oxygen (paO_2) and carbon dioxide ($paCO_2$) (via pulse oximetry and capnography) [73,74]. While there is no universal guideline on assessment timing, it is widely accepted that testing should be repeated every 6 to 12 months in symptomatic patients, or more frequently (every 3-6 months) in those requiring ventilation [75].
Polysomnography should be performed when symptoms of sleep disturbances are present, such as daytime sleepiness, unexplained fatigue, observed apneas during sleep, or snoring, or when vital capacity falls below 40-50% of the predicted value. Additionally, imaging techniques such as CT, T1-weighted MRI, and ultrasound of the diaphragm and accessory respiratory muscles have become valuable tools in both clinical and research settings for assessing respiratory involvement [73,76].
Therapeutic goals vary depending on the severity of the disease, ranging from improving or stabilizing vital capacity and respiratory muscle strength in less affected patients to reducing dyspnea, preventing infections, minimizing ventilation time, and generally improving quality of life in advanced cases [75]. When chronic respiratory failure develops, non-invasive ventilation (NIV) or invasive ventilation via tracheostomy should be started to improve gas exchange and reduce nocturnal hypoventilation, with overall benefits on survival. Cough assistance, including techniques such as manually assisted coughing, air stacking, and insufflation/exsufflation, is required when peak cough flow (PCF) values fall below 270 L/min to optimize airway clearance [5].
Real-world, longitudinal data on ERT-treated patients indicate stability of FVC over a 5-year period, especially in patients who begin treatment earlier (i.e., at a younger age and with a shorter disease duration) [77]. Additionally, a registry-based study found that although FVC begins to decline after 5 years of therapy, its trajectory remains better than the natural history of the disease for at least 13 years of follow-up [78]. Furthermore, evidence suggests that adding respiratory rehabilitation to ERT may be beneficial. Respiratory muscle training (RMT), using devices that provide increasing resistance during breathing, has been shown to strengthen the diaphragm and improve MIP in LOPD patients treated with ERT [79]. Studies have found that the effects of RMT on MEP were less apparent and did not persist long-term (12-24 months), while improvements in MIP have been sustained for up to 52 weeks [80,81].

Cardiac function management

Glycogen deposition in the heart walls and along the atrioventricular conduction system (including the bundle of His, as well as the si-

noatrial and atrioventricular nodes) is rarely observed in LOPD and particularly pronounced in IOPD. This results in the onset of hypertrophic (or mixed) cardiomyopathy, heart failure, and arrhythmias [5].
According to the guidelines proposed by the American College of Medical Genetics (ACMG) Work Group on the Management of Pompe Disease in 2006, cardiac status should be initially assessed with an echocardiogram to evaluate the extent of cardiomyopathy and a 24-hour ambulatory ECG to detect life-threatening arrhythmias. These tests should be repeated at regular intervals (even though specific timeframes are not indicated), alongside routine chest X-rays, even in patients receiving enzyme replacement therapy (ERT) [5]. Certain ultrasound measurements, such as 2-D ejection fraction (EF) and left ventricular (LV) mass normalized to a z-score, are particularly useful for monitoring response to treatment. Additionally, drastic changes in fluid status, whether through dehydration or fluid overload, should be avoided, as should the use of beta-blockers due to reports of sudden death. The use of inotropes (e.g., digoxin), diuretics, or ACE inhibitors should be approached with caution due to the risk of worsening left ventricular outflow tract obstruction.

Nutrition and musculoskeletal management and rehabilitation

Nutritional management and motor rehabilitation are discussed together below, as many studies have evaluated the combined effects of both. Muscle degeneration, sometimes disproportionate to glycogen accumulation, may be related to concomitant proteolytic mechanisms, further supported by evidence of reduced levels of certain plasma amino acids following the ingestion of a protein load [82,83]. Therefore, approaches involving high-protein, low-carbohydrate diets have been explored in the past to provide the amino acid substrates necessary to counteract proteolysis and promote protein synthesis. Simultaneously, combining this with submaximal aerobic exercise aims to shift energy production toward fatty acid metabolism, reducing the need for glycogenolysis [84], and may help decrease type II fibers, which are more prone to autophagic vacuole formation and more resistant to ERT [85,86]. In addition, both nutrition (in terms of timing and specific amino acid intake) and exercise can promote autophagy, a common dysfunctional mechanism in the pathology of Pompe disease [87]. An earlier American study, conducted at the onset of ERT, evaluated the effect of a combined "nutrition and exercise therapy" (NET) protocol on the rate of muscle deterioration, as measured by the modified Walton scale, in a cohort of 26 naive LOPD patients [88]. The aerobic exercise program consisted of daily use of a treadmill (or a bicycle for non-ambulant patients) for 45-50 minutes, followed by an upper-body ergometer for 10-15 minutes, aiming to achieve 60%-65% of maximal oxygen consumption (VO_2 max) or maximal heart rate for age (corresponding to a rate of perceived exertion of 11-12, defined as mildly hard on the Borg scale). In terms of diet, patients were instructed to take 1.5 g of L-alanine 4 times a day, in addition to a diet with a caloric distribution of 25%-30% protein, 30%-35% carbohydrate, and 35%-40% fat. Both muscle and lung function (although not significantly for the latter) appeared to stabilize in patients who adhered to and complied with the NET. This was partly consistent with previous anecdotal reports in advanced patients showing a beneficial effect of a high-protein diet (enriched with branched-chain amino acids) on lung function, while others suggested that it did not lead to clear improvements in motor function, primarily due to non-compliance [89-94].
More recently, one Dutch and two Italian studies evaluated the efficacy of a combined diet and exercise approach in ERT-treated LOPD patients. The first study showed positive effects from a specific 12-week exercise training program on endurance, muscle strength, muscle function, and core stability, as well as on pain and fatigue (although the latter was independent of improvement in muscle strength), in a cohort of 23 patients [95,96]. The study by Sechi A et al. was a crossover design, with an initial control period (of 26 weeks) followed by a second intervention period (also 26 weeks), where patients underwent either exercise alone (moderate-intensity aerobic exercise on a cycle ergometer, stretching, balance exercises, and strength training) or a combination of exercise + diet (composed of 25-30% protein, 30-35% carbohydrate, and 35-40% fat) [97]. Thirteen patients on ERT for an average of 6 years participated, with a compliance rate of over 70%. They showed a decrease in exercise tolerance (measured by peak aerobic power) during the control period, followed by an increase during the intervention, particularly in the combined exercise + diet group. Markers of muscle damage, pulmonary function, and quality of life also significantly improved during the combined intervention.
The second study, which enrolled 58 LOPD patients who had been on ERT for at least two years, showed that patients who regularly followed both diet and exercise accounted for only 20% of non-responders (self-defined as those who had worsened or remained stable) and 47% of responders (those who had improved) [98]. On the other hand, patients who reported following only one of the two interventions (diet or exercise) or neither regularly accounted for 80% of non-responders and 53% of responders. However, this study did not find an association between BMI at baseline and treatment response. Similar positive results have also been found in the paediatric Pompe disease population, as described in a recent paper on 14 children (mean age: 10.6 years), of whom 6 had IOPD. These children showed improvements in muscle strength, core stability, quality of life, and parent-reported fatigue thanks to a lifestyle intervention including physical training and a high-protein diet (2 g/kg) [99].
Despite the individual studies mentioned above, there is a lack of consistency in the exercise protocols offered to patients. It has been demonstrated that muscle strength declines over a 1-year period by 7.1% in the lower limbs and 4% in the upper limbs [72].
According to the 2006 American College of Medical Genetics (ACMG) Guidelines for the Diagnosis and Management of Patients with Pompe Disease, muscle function must be improved through submaximal aerobic exercise, avoiding resistive and eccentric exercise and preventing overexertional weakness [5].
These concepts were adopted and integrated in 2012 by the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) consensus on the management and treatment of LOPD, which emphasized maximizing the benefits of ERT [100]. The main recommendations were to preserve motor function, prevent secondary complications, and promote general health and quality of life. This should be achieved through moderate to vigorous aerobic exercise, up to 60-70% of max-

imal effort, 3-5 days per week. The daily routine should also include gentle stretching to limit contractures and deformities and correcting poor posture with appropriate orthotics before tendon tightness and chronic musculoskeletal pain develop. As highlighted by a recent Italian study, operational protocols should be tailored to the stage of disease, favouring adapted physical activity (ranging from ADL to sport in appropriate, supervised settings) for patients with mild impairment, and individual rehabilitation plans based on therapeutic exercise for patients with more sever functional limitations [101].

Regarding scoliosis, the consensus is that surgical intervention, preceded by pulmonary function testing and followed by aggressive post-operative ventilatory support, is indicated when the Cobb angle is between 30° and 40°, as this is essential to improve sitting balance [100]. Additionally, all LOPD patients should be screened annually with dual-energy X-ray absorptiometry (DEXA), undergo fall risk assessment, and take vitamin D and calcium supplements to counteract osteopenia and osteoporosis, conditions affecting 67% of patients [102].

During the 208th European Neuromuscular Centre international workshop, another unmet need was addressed: the identification of effective and common outcome measures that accurately reflect changes resulting from rehabilitation treatment [103]. The minimum dataset included the assessment of motor function (using the Medical Research Council grading scale, hand-held dynamometry, or quantitative muscle testing for muscle strength, and 6-minute walk test [6MWT] and timed tests, including walking 10 meters, climbing four steps, standing up from a supine position, and standing up from a chair for muscle function) and pulmonary function (forced vital capacity [FVC] standing and sitting, maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], ventilatory status). The importance of patient-reported outcomes (PROs), such as the Rasch-built Pompe-specific activity scale and the Fatigue Severity Scale (FSS), was also emphasized.

Management of central nervous system involvement

The evidence of glycogen accumulation in both grey (cortical brain, brainstem, and cerebellar neurons; spinal anterior horn cells) and white (glial cells and astrocytes) matter necessitates consideration of potential alterations in the central nervous system (CNS) in individuals with Pompe disease [104]. For instance, hearing loss has been recognized in IOPD patients, attributed to direct involvement of the cochlea (though rare) or the conductive apparatus [105]. Children with Pompe disease should undergo baseline and annual hearing tests, including otoacoustic emissions, tympanometry, and Auditory Evoked Potentials (ABR/BAER). Regarding cognitive function, there are no clear guidelines for screening methods, but clinicians should be aware that some developmental delays, along with mild intellectual disabilities, may occur in long-term IOPD survivors treated with enzyme replacement therapy (ERT), in whom periventricular white matter abnormalities are observed on brain imaging [106-109]. In contrast, functional brain changes, including disruption of neuronal networks, and mild neuropsychological dysfunction are more commonly seen in LOPD [110,111].

Vascular involvement in the intracranial blood vessels (basilar artery, internal carotid artery, and medial cerebral arteries) should also be considered in the assessment and serial MRI angiograms should be scheduled during the follow-up [112]. The weakening of vascular smooth muscle leads to dolichoectasia and the formation of aneurysms; CNS vascular abnormalities seem to correlate with age and disease duration, but not with the severity of muscle/respiratory involvement or with genetic data [113].

Discussion

The results of these narrative reviews clearly indicate that, beyond the promising therapeutic successes of enzyme replacement therapy and the potential of gene therapy on the horizon, there is a lack of clear guidance on the multidisciplinary management of the rehabilitative (motor and respiratory), nutritional, and systemic aspects of Pompe disease. Most of the evidence in these areas comes from experimental studies conducted on small, heterogeneous patient cohorts.

First and foremost, there is an urgent need to establish common definitions of disability, whether motor or respiratory. This would allow these functions to be included in standardized classification systems, based on which rehabilitation protocols can be developed and regulated across many European countries. This approach should go hand in hand with the identification of accurate and reliable outcomes for clinical trials.

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