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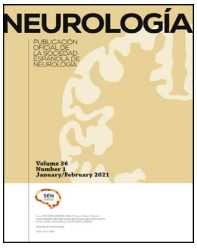

CONSENSUS STATEMENT

Recommendations for the diagnosis, treatment, and follow-up of late-onset Pompe disease

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Abstract Pompe disease or glycogenosis type II is a rare disease caused by mutations in the GAA gene that leads to deficiency of the acid alpha-1,4-glucosidase enzyme. As a result of the enzymatic defect, a progressive accumulation of intralysosomal glycogen occurs in various tissues, causing smooth, cardiac and skeletal muscle involvement. When the age of onset of the disease is after the first year of life, it is called late-onset Pompe disease (LOPD). Weakness of the axial and proximal waist muscles and respiratory dysfunction are common manifestations. Enzyme replacement therapy (ERT) has been available for more than 15 years and is the standard treatment. This therapy changes the course of the disease, although the effectiveness of the treatment reduces over time. New enzyme therapies represent new treatment opportunities for patients with LOPD. Here we present updated recommendations from a group of experts in Pompe disease on the diagnosis, treatment and follow-up of LOPD patients, with the aim of providing a guide for the clinical management of the disease.
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PALABRAS CLAVE
Afectación respiratoria;
Alfa glucosidasa ácida;
Debilidad muscular;
Enfermedad de Pompe;
Inicio tardío;
Terapia enzimática sustitutiva

Recomendaciones para el diagnóstico, tratamiento y seguimiento de la enfermedad de Pompe de inicio tardío

Resumen La enfermedad de Pompe o glucogenosis tipo II es una enfermedad poco frecuente causada por mutaciones en el gen *GAA* que conduce a la deficiencia de la enzima alfa-1,4-glucosidasa ácida. Como resultado del defecto enzimático se produce una acumulación progresiva de glucógeno intralisosomal en diversos tejidos, causando afectación del músculo liso, cardíaco y esquelético. Cuando la edad de inicio de la enfermedad es posterior al primer año de vida se denomina enfermedad de Pompe de inicio tardío (LOPD) y tiene como principales manifestaciones clínicas la debilidad de la musculatura axial y proximal de cinturas y la disfunción respiratoria. El tratamiento estándar con la terapia enzimática sustitutiva (ERT), disponible hace más de 15 años, consigue cambiar el curso de la enfermedad, aunque la eficacia del tratamiento se ve reducida con el paso del tiempo. Las nuevas terapias enzimáticas suponen nuevas oportunidades de tratamiento para los pacientes con LOPD. Este trabajo presenta recomendaciones actualizadas de un grupo de expertos en la enfermedad de Pompe sobre el diagnóstico, tratamiento y seguimiento de pacientes LOPD, con el objetivo de proporcionar una guía para el manejo clínico de la enfermedad.
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Introduction

Pompe disease or glycogen storage disease type II (GSD II) is a rare autosomal recessive genetic disease. It is caused by a deficiency of the enzyme acid α-1,4-glucosidase (GAA), encoded by the *GAA* gene, located on the long arm of chromosome 17 (17q25.3). GAA is responsible for intralysosomal glycogen hydrolysis, and absence or deficiency of the enzyme results in progressive accumulation of glycogen in various tissues, although symptoms are typically caused by involvement of skeletal, smooth, and/or cardiac muscle.[1,2]

Pompe disease is classified into 2 categories, according to the age of symptom onset and the presence of cardiomyopathy. Classic infantile-onset Pompe disease (IOPD) is caused by absent or severely reduced GAA activity, generally below 1% of normal levels. Late-onset Pompe disease (LOPD) is caused by a reduction in GAA activity to 1%-30% of normal levels.[3]

Patients with IOPD develop symptoms within the first year of life, and rarely survive beyond 18 months of age if the condition is left untreated. The main clinical manifestations include hypotonia, generalised muscle weakness, dysphagia, progressive respiratory failure, hypertrophic cardiomyopathy, hepatomegaly, and macroglossia.[1,4] Cases have been reported of symptom onset during the first year of life without associated hypertrophic cardiomyopathy; these cases have been described as non-classic infantile-onset forms.[1,4] Cases with symptom onset after the first year of life and without relevant cardiac involvement are classified as LOPD. Symptoms may manifest during childhood, adolescence, or adulthood. The main clinical manifestations of LOPD include progressive axial and proximal limb girdle muscle weakness, with early involvement of respiratory muscles. Early symptoms, before the onset of weakness, may be non-specific and include exercise intolerance and fatigue. In this phase, most patients present persistently elevated creatine kinase (CK) levels, which may facilitate early diagnosis of the disease. Motor impairment is slowly progressive, and accompanied by respiratory failure, leading to loss of independent walking and the need for mechanical ventilation. Respiratory problems are the main cause of morbidity and mortality associated with the disease, and often precede the loss of independent walking.[4]

The objective of this study is to review and update the existing recommendations on the diagnosis, treatment, and follow-up of LOPD, incorporating new knowledge from over 15 years' experience with enzyme replacement therapy (ERT) and the recent appearance of new enzyme therapies.[5–11] These updated recommendations are intended to facilitate and to harmonise as far as possible the clinical management of the disease by the professionals involved.

Material and methods

These recommendations are the outcome of a review of the existing guidelines and recommendations in the literature[5–11] and a Delphi panel that sought to establish the greatest possible consensus among a multidisciplinary team comprising 19 experts specialising in pulmonology, paediatric neurology, inborn errors of metabolism, neurology, and internal medicine. Three questionnaires were developed, with a total of 38 questions addressing the diagnosis, treatment, and follow-up of LOPD; members of the expert panel responded electronically. Issues for which no consensus was established in the initial questionnaire were discussed in a teleconference until a consensus was reached in the final recommendations.

Results

Diagnosis

As Pompe disease is a treatable disease that may lead to premature death, its early diagnosis is highly important. Diagnosis can be complex, given the clinical heterogeneity of late-onset forms.[9]

Analysis of GAA enzyme activity

In patients with suspected Pompe disease, the recommended screening test is a dried blood spot (DBS) enzyme analysis of GAA.[9] Suspicion of Pompe disease is based on a set of signs and symptoms compatible with the disease, including elevated serum CK levels, progressive muscle weakness (particularly affecting limb girdle or axial muscles), and/or neuromuscular respiratory involvement.[6]

DBS determination of enzyme activity is a rapid, accessible, and highly sensitive test; however, as it may yield false positive results, results must be confirmed when low enzyme activity is observed.[6] It should be noted that carriers of a single variant (*GAA* mutation in heterozygosity) may also present enzyme activity in the pathological range, as demonstrated in some studies[12,13]; therefore, results should be interpreted with caution.

Electromyography may display a myopathic pattern with myotonic discharges, particularly in paraspinal muscles, even in the absence of clinical myotonia. However, presence of electrical myotonia is not specific to Pompe disease, and may also be observed in such other muscle diseases as myotonic dystrophy types I and II, channelopathies, myofibrillar and toxic myopathies, etc.[4,6,14]

A genetic study must be performed to confirm the diagnosis.[10] In addition to point mutations in the *GAA* gene sequence, large deletions, duplications, and deep intronic variants have also been described, and should be taken into consideration in the genetic study. Therefore, if results from direct sequencing (Sanger or next-generation sequencing) are inconclusive, further studies should be performed to detect gains or losses of genetic material, including in intronic regions.[3]

A useful guide for evaluating the pathogenicity of *GAA* variants is the Erasmus Center database (https://www.pompevariantdatabase.nl), which includes 911 known variants of the *GAA* gene, 648 (71%) of which are pathogenic; of these, the genotype-phenotype correlation is known for 336 (database consulted 18 April 2024).[15,16] When a complete genetic study does not identify biallelic pathogenic variants and Pompe disease is strongly sus-

pected, analysis of GAA activity in different tissues may be helpful in supporting diagnosis.[8] Enzyme analysis in fibroblast cultures obtained from skin biopsy is considered the gold standard test, although the procedure is somewhat invasive and results may take up to 6 weeks. Some studies suggest that the results of blood enzyme analysis are comparable to those of fibroblast studies; furthermore, the study is faster and less invasive.[14,17] Enzyme analysis may also be performed in skeletal muscle, if tissue samples are available.

Genetic studies of family members at risk

Genetic counselling of all family members is recommended; genetic studies should be performed for family members at risk of developing or carrying the disease. When these individuals are minors, the need for the genetic study should be discussed with their parents or legal representatives. The detection of carriers of pathogenic variants facilitates family planning.[10]

Muscle magnetic resonance imaging

Muscle MRI studies may be used to evaluate the distribution and severity of muscle involvement in LOPD; T1-weighted sequences enable detection of fatty replacement of muscles, and STIR sequences reveal oedema of the affected muscles. T1-weighted sequences display a characteristic pattern of fatty replacement that is useful for diagnosis, and may help to select which muscle to target in the biopsy study, if this study is needed.[4] The typical pattern on T1-weighted sequences is characterised by fatty replacement of the following muscles: tongue, subscapular muscles, paraspinal and abdominal muscles, gluteus medius and minimus, posterior thigh muscles, adductor magnus, and vastus intermedius.[18,19] Distal muscles of the legs are generally spared. A strong correlation has been shown between muscle strength, functional motor scales, and the degree of fatty replacement observed on muscle MRI; furthermore, the first signs of fatty replacement may precede muscle weakness in patients studied due to hyperCKaemia.[18] Detection of a progressive increase in the replacement of skeletal muscle with adipose tissue may also be taken into account before starting ERT in paucisymptomatic patients.[18]

Muscle biopsy

Muscle biopsy may support the diagnosis of Pompe disease. However, results may be non-specific or even normal in patients with late-onset forms, especially if the tissue sample is taken from an unaffected muscle. Thirty percent of patients with LOPD are estimated to present normal or non-specific forms.[6,9] It is important that specimens are correctly stored and that freezing, fixing, embedding, and staining are optimal.[20] Periodic acid-Schiff (PAS) staining in semithin sections is the most reliable method for detecting vacuoles with glycogen accumulation, regardless of size. However, this technique is not available at all laboratories, and results are non-specific. Acid phosphatase staining may also help to identify the accumulation of lysosomal material in the sarcoplasm of muscle fibres, even in biopsy specimens with no clear evidence of vacuole formation or other structural changes.[9,20,21]

Assessment of potential vascular complications

Though they are rare, cardiovascular alterations and vascular malformations have been documented.[22] Therefore, it is advisable after diagnosis to discuss with patients the potential risks of vascular complications and the possibility of conducting diagnostic tests to detect them.[20,23,24]

Vascular abnormalities can be detected with CT angiography and MR angiography. These techniques should be used to study the cerebral vessels, supra-aortic trunks, and the aorta and its main branches. CT angiography is more advisable, particularly in patients with respiratory failure, as it is faster and more convenient. However, in patients who can tolerate longer tests, MR angiography is more suitable due to the lower exposure to radiation. If an intracranial aneurysm is detected, the risk of rupture and the need for endovascular treatment should be assessed.[20]

Cardiac involvement is very rare in LOPD. One study reported short PR interval in 10% of patients, reduced left ventricle systolic function in 7%, and mildly elevated left ventricular mass in 5%; in another study, 13% of patients had some degree of heart hypertrophy. Furthermore, cases have been reported of patients with LOPD presenting heart rhythm alterations, including sinus arrhythmia, supraventricular tachycardia, Wolff-Parkinson-White syndrome, and atrioventricular block.[32] Electrocardiography and 24-h Holter monitoring can rule out such cardiac arrhythmias as Wolff-Parkinson-White syndrome, which is also associated with a short PR interval, and second-degree atrioventricular block,[20] whereas echocardiography is used to assess ventricular structure and function.[4,14]

Diagnosis of respiratory involvement in Pompe disease

Patients with LOPD may present respiratory muscle weakness, even before the onset of significant limb weakness. Respiratory problems are the main cause of morbidity and mortality in Pompe disease.[9,25]

Progressive respiratory muscle weakness causes a pattern of shallow breathing, and greater workload and risk of muscle fatigue, leading to alveolar hypoventilation, which is initially nocturnal and may progress to daytime hypoventilation. Furthermore, respiratory muscle weakness, mainly involving intercostal and abdominal muscles, causes ineffective cough alongside impaired airway protection due to an alteration in the oropharyngeal muscles, contributing to ineffective cough and swallowing and voice disorders.[26]

Symptoms related to respiratory muscle weakness include dyspnoea, both on exertion and at rest; reduced physical capacity; episodes of bronchoaspiration; and respiratory tract infections. Furthermore, some symptoms associated with nocturnal hypoventilation include interrupted sleep, excessive daytime sleepiness, and fatigue.[9,25]

Given the great variability in disease progression and diaphragm disorders, it is highly important to evaluate and monitor patients' respiratory function from the time of diagnosis.[25,27]

Initial assessment

After diagnosis of Pompe disease, patients should undergo assessment and follow-up at specialised pulmonology consultations within multidisciplinary neuromuscular disease units. In addition to respiratory function testing, specific studies should be performed to rule out sleep-related breathing disorders, which may appear early in the progression of the disease.

The recommended tests include forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), sniff nasal inspiratory pressure (SNIP), cough peak flow, night-time oxycapnography, and blood gas analysis (Table 1).[25,26]

FVC should be tested in both seated and supine positions, and is able to detect restrictive ventilatory defects due to inspiratory muscle weakness. Seated FVC is considered to be reduced when the value is below 80% of the reference value. A drop of greater than 20% in supine as compared to seated FVC suggests the presence of significant diaphragm weakness.[25,26,28]

MIP and MEP are tests that measure the strength of inspiratory and expiratory muscles, respectively. MIP measures the maximal pressure during forced inspiration from residual volume, against an occluded airway (Müller manoeuvre). MIP is considered pathological if the value is below 50% of the expected value and/or greater than −80 cm H_2O. MEP measures the maximal pressure during forced expiration from total lung capacity, against an occluded airway (Valsalva manoeuvre). MEP is considered pathological if the value is below 50% of the expected value and/or below 90 cm H_2O.[25,26,29]

SNIP measures the maximal pressure generated when sniffing with one nasal cavity blocked. The test is not invasive, and may be considered in addition or as an alternative to MIP in patients with facial weakness or poor mouth closure. SNIP values below 40 cm H_2O are considered pathological.[25,26]

Cough peak flow is used to assess the efficacy of expiratory muscles in eliminating secretions. Healthy adults present values greater than 350 L/min, with values below 270 L/minute indicating that coughing is ineffective in eliminating secretions.[26]

Night-time oxycapnography enables non-invasive, real-time monitoring of oxygen saturation (SpO_2) and transcutaneous carbon dioxide pressure ($tcPCO_2$), which offers information about alveolar ventilation and may detect periods of nocturnal hypoventilation. Capnography results are considered pathological if peak $tcPCO_2$ is greater than 49 mm Hg or if mean $tcPCO_2$ is greater than 50 mm Hg. Hypoventilation is defined as SpO_2 values below 90% for over 10% of the time or below 88% for more than 5 consecutive minutes.[25,26,28]

Arterial blood gas analysis can determine oxygenation, ventilation, and acid-base status based on measurement of partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), arterial oxygen saturation (SaO_2), and pH. Daytime hypercapnia is defined as pCO_2 > 45 mm Hg in the baseline arterial blood gas study.[25,26]

Such imaging tests as diaphragm ultrasound and MRI may help to evaluate diaphragm function. Ultrasound can be used to measure the thickness of the diaphragm and to evaluate its movement, whereas MRI can be used to assess diaphragm kinetics.[25,26] Diaphragm ultrasound and MRI are recommended as optional complementary tests. The diaphragm thickening fraction is the change in diaphragm thickness between the end-inspiration and expiration, with respect to thickness at end-expiration.[30] A thickening fraction below 20% is considered to indicate diaphragm dysfunction.[31] With regard to MRI, no consensus currently exists on normative values or what values should be considered pathological.[25]

Recommendations for the diagnosis of late-onset Pompe disease

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- DBS analysis is recommended in patients with asymptomatic hyperCKaemia and suspected myopathy, particularly if they present limb girdle and/or axial muscle weakness and/or neuromuscular respiratory involvement.
- In patients showing reduced enzyme activity on DBS, results should be confirmed with a whole blood analysis and genetic testing.
- In patients presenting low enzyme activity by negative genetic sequencing results, an extended genetic study is recommended.
- Muscle biopsy is recommended for patients with suspected Pompe disease with negative genetic study results.
- Muscle MRI can reinforce diagnostic suspicion and may support treatment onset.
- Once a diagnosis of Pompe disease is established, genetic studies are recommended for all family members at risk of developing or carrying the disease. In patients of minor age, the case should be discussed with their parents and/or legal representatives.
- After diagnosis, potential vascular complications of the disease should be discussed with patients with a view to performing diagnostic tests to detect vascular alterations.

Diagnosis of respiratory involvement

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- Patients should be referred to the pulmonology department from the time of diagnosis, regardless of their symptoms.
- The recommended tests for the initial assessment of patients with Pompe disease include seated and supine FVC, MIP and MEP, SNIP, cough peak flow, night-time oxycapnography, and blood gas analysis.
- Diaphragm ultrasound and/or MRI are optional complementary tests in the initial patient assessment.

Treatment

The standard treatment for Pompe disease, available since 2006, is ERT with recombinant human acid alglucosidase alfa (rhGAA). ERT is administered by intravenous infusion dosed at 20 mg/kg every 2 weeks, and is indicated for

Table 1 Recommended tests for the initial assessment of patients with Pompe disease and pathological results.[25,26,28]

		Pathological results
Recommended tests	Seated and supine FVC	Seated FVC < 80% and/or > 20% drop in supine FVC
	MIP	MIP < 50% and/or < −80 cm H_2O
	MEP	MEP < 50% and/or < 90 cm H_2O
	SNIP	SNIP < 40 cm H_2O
	Cough peak flow	Cough peak flow < 270 L/min
	Night-time oxycapnography	Peak $tcPCO_2$ > 49 mm Hg
		Mean $tcPCO_2$ > 50 mm Hg
		Overnight pulse oximetry with CT90 > 10%
		Overnight pulse oximetry with SpO_2 < 88% for > 5 consecutive minutes
Optional tests	Blood gas analysis	Baseline arterial blood gas study with pCO_2 > 45 mm Hg
	Diaphragm ultrasound and/or MRI	Diaphragm ultrasound showing thickening fraction < 20%

CT90: cumulative time with SpO_2 < 90%; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; SNIP: sniff nasal inspiratory pressure; pCO_2: partial pressure of carbon dioxide; SpO_2: peripheral oxygen saturation; $tcPCO_2$: transcutaneous partial pressure of carbon dioxide.

patients of all ages with confirmed diagnosis of Pompe disease.[33]

In LOPD, ERT has been demonstrated to improve or stabilise motor and respiratory function, to reduce the risk of loss of independent walking, and to prolong survival.[34]

After diagnosis of LOPD, the decision to start ERT depends on the patient's clinical status. Immediate onset of ERT is generally recommended in symptomatic patients presenting muscle weakness in the physical examination or low values in the respiratory function assessment, independently of the use of non-invasive mechanical ventilation (NIMV). Presence of such symptoms as sleep apnoea/hypopnoea or dyspnoea on exertion is only considered sufficient to start treatment if they are associated with objective evidence of respiratory dysfunction.[35]

On the other hand, asymptomatic patients with no objective signs of disease should be regularly monitored, with a view to starting treatment in the event of clinical impairment of muscle strength or pulmonary function.[35] Muscle MRI evidence of progressive replacement of muscle tissue with adipose tissue may be taken into account when considering treatment onset.[18]

Following ERT onset, patients should be monitored to assess treatment response.[35]

Home treatment

The quality of life of patients with LOPD may be negatively affected by the significant amounts of time they must dedicate to receiving treatment. Enzyme therapy can be administered at home; this offers patients greater independence and flexibility, and reduces the impact on their daily life. A study of 121 patients with LOPD showed that home administration of ERT is safe when appropriate protocols are put in place for treatment administration and management of reactions to the infusion, and when trained healthcare professionals are available.[36] Therefore, home treatment is recommended after good tolerance of the infusion is confirmed at hospital.

Switching enzyme replacement therapies

While over 90% of patients benefit from ERT, they generally show the greatest clinical benefit during the first 3-5 years of treatment, which is followed by a slow worsening in at least half of cases.[37] The reasons for the limited efficacy and short duration of the effect of ERT remain unclear, although numerous factors may be at play: for instance, skeletal muscle presents low density of mannose-6-phosphate (M6P) receptors, limiting the enzyme's uptake and access into the tissue; the enzyme is active in an acidic medium, and therefore preferentially acts on intralysosomal rather than cytoplasmic glycogen; established lysosomal and mitochondrial dysfunction is not corrected by exogenous administration of the deficient enzyme and may also interfere with uptake and targeting of the enzyme at the lysosome. These limitations have led to a search for new therapies. One of the strategies followed has been to optimise ERT. Two new enzyme therapies have recently been commercialised.

Firstly, avalglucosidase alfa is an rhGAA with an increased number of M6P residues, conferring a high affinity for the cell surface M6P receptor and improving its uptake by muscle fibres.[38] The COMET study, a multicentre, international, phase III clinical trial, showed that avalglucosidase alfa is not inferior to alglucosidase alfa, presenting better clinical outcomes in respiratory and motor function. That study included 100 treatment-naïve patients with LOPD, who were randomly allocated to receive alglucosidase alfa or avalglucosidase alfa over a 49-week period, followed by an open-label extension phase in which all patients received avalglucosidase alfa treatment. Compared to the alglucosidase alfa group, patients treated with avalglucosidase alfa displayed a greater nominal increase in FVC (2.89% vs 0.46%) and walked further in the 6-minute Walk Test (6MWT;

32.21 vs 2.19 m) at 49 weeks of follow-up. The differences in the 6MWT were statistically significant to demonstrate non-inferiority between treatments ($P = .0074$), but did not achieve statistical superiority ($P = .06$). Avalglucosidase alfa also showed a favourable safety profile.[35,38]

Another novel treatment is the combination of cipaglucosidase alfa plus miglustat, which acts to stabilise the enzyme. Unlike avalglucosidase alfa, which is indicated for the treatment of all types of Pompe disease, cipaglucosidase alfa plus miglustat is only indicated for adult patients with LOPD.[39–41] This recombinant enzyme also displays greater affinity for the cation-independent M6P receptor.[42] The PROPEL study, a multicentre, international, phase III clinical trial, showed that, compared with patients under treatment with alglucosidase alfa, patients treated with cipaglucosidase alfa plus miglustat achieved a greater increase in the distance in the 6MWT (20.0 vs 8.3 m) and lesser worsening in FVC (−1.4% vs −3.7%) at 52 weeks of follow-up; however, these differences were not statistically significant.[40,42] This study included both naïve patients (n = 27) and patients already under treatment with alglucosidase alfa (n = 95), who were randomly assigned at a 2:1 ratio to receive cipaglucosidase alfa plus miglustat or to maintain treatment with alglucosidase alfa for 51 weeks. When results were analysed according to previous ERT, naïve patients presented better motor and pulmonary function outcomes with alglucosidase alpha. Patients receiving cipaglucosidase alfa plus miglustat displayed an improvement of 28.5 m in 6MWT performance, compared to 52.7 m in the alglucosidase alfa group. Furthermore, the cipaglucosidase alfa plus miglustat group presented greater deterioration in FVC than the alglucosidase alfa group (−5.2% vs −2.4%). On the other hand, patients previously treated with ERT who switched to cipaglucosidase alfa plus miglustat presented a greater mean improvement in 6MWT performance (15.9 vs 1.0 m) and a smaller deterioration in FVC (−0.2% vs −3.8%) than patients who continued alglucosidase alfa treatment.[40] The incidence of adverse events was similar in both treatment groups, with falls, headache, nasopharyngitis, myalgia, arthralgia, and nausea being the most frequent events.[42] It should be noted that combined treatment with cipaglucosidase alfa plus miglustat is not recommended for women of childbearing age and not using reliable contraceptives, or during pregnancy or breastfeeding, due to contraindications associated with miglustat.[41]

Therefore, both new enzyme therapies have been shown to be at least as effective and safe as alglucosidase alfa, at least during the first year of treatment. Furthermore, the benefits of avalglucosidase alfa have been shown to persist in the long term with continued treatment, as observed in the open-label extension phase of the COMET trial. Participants in that study were treated with avalglucosidase alfa from weeks 49–145. Patients switching from alglucosidase alfa to avalglucosidase alfa presented a mean change of 0.7% in FVC testing (95% CI, −1.4% to 2.8%) and a mean change of −2.3 m in the 6MWT (95% CI, −23.2 to 18.7) between weeks 49 and 145, whereas those initially receiving avalglucosidase alfa maintained the improvement in pulmonary and motor function observed at week 49.[39] Therefore, switching to one of the new ERT drugs is recommended for patients under treatment with alglucosidase alfa and presenting disease progression.[35] No study has compared the efficacy of the 2 new treatments, and we are therefore unable to recommend either drug as the first choice. For both drugs, treatment should be maintained for at least 12 months to evaluate their efficacy before a switch may be considered. In isolated cases with significant objective deterioration, switches may be considered before 12 months.

Increasing ERT dosage

The standard dose of alglucosidase alfa is 20 mg/kg; however, clinical worsening has been reported in patients with IOPD despite receiving the recommended treatment. Patients with IOPD and receiving high doses of alglucosidase alfa (40 mg/kg per week) show better survival than those receiving the standard dose. Higher doses have also been associated with a tendency towards better motor function.[43,44] Doubling the dose of ERT has also been shown to be beneficial in paediatric patients with LOPD. ERT at doses of 40 mg/kg has been shown to be safe and effective, with patients displaying improvements in motor and pulmonary function.[45]

These results support increasing doses from 20 to 40 mg/kg/week in paediatric patients showing worsening of symptoms after an initial improvement with ERT; however, insufficient data are available to support increasing the dose in adult patients.

Anti-ERT antibody determination

The formation of IgG antibodies against ERT is a known effect of treatment. In Pompe disease, the majority of patients treated with ERT develop anti-GAA antibodies, although levels are low. It is very rare for these antibodies to neutralise the effect of treatment in patients with LOPD[46]; however, their level should be determined in patients with poor response to ERT.[8,47]

Treatment in patients with respiratory involvement

Although ERT improves patients' quality of life and survival, motor and respiratory function may continue to deteriorate and patients often require invasive or non-invasive mechanical ventilation.[1,4]

Non-invasive mechanical ventilation

It is essential to ensure appropriate daytime and nocturnal ventilation, providing ventilatory support where needed.

Non-invasive mechanical ventilation should be considered in patients with symptoms suggestive of hypoventilation (eg, daytime sleepiness, morning headache, and morning malaise) or diaphragm involvement (eg,

Table 2 Criteria for indication of mechanical ventilation.[25,26,28]

Indications for NIMV
[•]Symptoms suggestive of hypoventilation: daytime sleepiness, morning headache, morning malaise
• Symptoms suggestive of diaphragm involvement: orthopnoea
• Daytime hypercapnia
• Peak $tcPCO_2$ > 49 mm Hg and/or mean $tcPCO_2$ > 50 mm Hg
• Seated FVC < 80% and/or > 20% drop in supine FVC
• SNIP < 40 cm H_2O
• MIP < 50% and/or < −60 cm H_2O
• Overnight pulse oximetry with SpO_2 < 88% for > 5 consecutive minutes and/or SpO_2 < 90% for over 10% of the time (CT90 > 10%)
Indications for invasive mechanical ventilation
[•]NIMV is not effective in correcting nocturnal hypoventilation
• Bronchial secretions are poorly managed despite adequate treatment

CT90: cumulative time with SpO_2 < 90%; FVC: forced vital capacity; MIP: maximal inspiratory pressure; NIMV: non-invasive mechanical ventilation; SNIP: sniff nasal inspiratory pressure; SpO_2: peripheral oxygen saturation; $tcPCO_2$: transcutaneous partial pressure of carbon dioxide.

orthopnoea), as well as daytime hypercapnia or pathological findings in capnography or other functional tests (Table 2).[25,26,28]

In patients with LOPD presenting respiratory involvement at onset in the form of acute respiratory failure, treatment should immediately be started with appropriate ventilatory support, and need to adapt treatment with home respiratory support and onset of ERT should be considered.

Invasive mechanical ventilation

Invasive mechanical ventilation (IMV) should be considered when NIMV is not effective in correcting nocturnal hypoventilation or when bronchial secretions are poorly controlled despite appropriate treatment (Table 2).[25,26,28]

However, the decision to start IMV must be taken on an individual basis, taking into account the potential involvement of other organs and the support required by the patient.

Comprehensive patient management

Management of patients with Pompe disease requires a comprehensive, multidisciplinary approach, as well as specific treatment with ERT.[7] General measures may include correct immunisation, good clearance of secretions, promoting maintenance of the patient's functional capacities, and ensuring adequate nutrition.

Correct immunisation is achieved through proper adherence to the vaccination schedule, as well as administration of pneumococcal and influenza vaccines, and prophylactic treatment against respiratory syncytial virus.[6,14] Vaccination against COVID-19 is also recommended in patients with LOPD, as they are a risk population for the disease.

Patients with respiratory muscle weakness present reduced airway clearance due to ineffective cough. This increases the risk of respiratory tract infections and the rates of morbidity and mortality associated with acute respiratory processes. Mechanisms for the proper drainage of secretions include manually assisted coughing and mechanically assisted coughing. If poor secretion management is suspected, cough peak flow measurement is recommended. In patients with values lower than 270 L/min, the need for assisted coughing should be assessed, and the tolerability and effectiveness of both mechanically and manually assisted coughing should be tested in order to identify the most indicated technique.[26,48]

Independently of respiratory involvement, prophylactic respiratory physiotherapy is recommended with a view to maintaining thoracic and pulmonary compliance and avoiding the appearance of microatelectasis.[26] Respiratory physiotherapy aims to stimulate secretion clearance through cough assistance devices (cough assist in-exsufflators), percussive manoeuvres (clapping), vibrations, postural drainage, and training of respiratory muscles to improve resistance.[49,50] Furthermore, rehabilitation, occupational therapy, and physiotherapy favour maintenance of the patient's functional capacities, in addition to the improvement in respiratory symptoms, speech disorders, and dysphagia.[14]

Aerobic exercise is also recommended. Some studies suggest that the combination of aerobic exercise and core strength and stability training improve strength, stabilisation capacity of the axial muscles, and muscle function.[51,52] Patients should perform submaximal, functional, and aerobic exercise regularly, combining aerobic and strength training.

Finally, patients with progressive neuromuscular diseases are often less physically active and expend less energy than active individuals. As a result, many patients with LOPD present sarcopenic obesity, with low muscle mass and a high percentage of fat.[52] Furthermore, some complications of the disease, such as dysphagia, may hinder food intake.[9]

Good monitoring of nutritional status is needed, with the use of alternative pathways when oral feeding is insufficient or unsafe. Diet must provide sufficient calories and be rich in proteins to prevent the loss of muscle mass.[8,9]

Recommendations for the treatment of late-onset Pompe disease

[•]
- ERT should be started in patients with objective symptoms of muscle and/or respiratory involvement.
- After good tolerance to ERT is confirmed at the day hospital, home treatment may be considered.
- Switching to another ERT is recommended if the patient shows a lack of response or progressive clinical worsening.
- In paediatric patients diagnosed with LOPD whose symptoms worsen after an initial improvement with ERT, the dosage may be doubled.
- It is advisable to test for anti-ERT antibodies in patients with no evidence of improvement or presenting significant clinical worsening.
- Vaccination against influenza, COVID-19, and pneumococcal disease is recommended.
- Respiratory physiotherapy should always be recommended in patients with LOPD, independently of the presence of respiratory involvement.
- Regular physical exercise is also recommended.

Treatment in patients with respiratory involvement

[•]
- Non-invasive mechanical ventilation should be considered in patients with symptoms or with pathological results in functional tests and hypercapnia or pathological capnography results.
- IMV should be considered when:

[○]
- ○ NIMV is not effective in correcting nocturnal hypoventilation.
- ○ Bronchial secretions are poorly managed despite adequate treatment.
- ○ Indication of IMV must be considered on an individual basis.
- In patients with suspected poor secretion management due to ineffective cough, it is advisable to measure cough peak flow and to test the tolerance/effectiveness of manually or mechanically assisted coughing.

Follow-up

Periodic follow-up of all cases of LOPD, whether symptomatic patients receiving treatment with ERT or asymptomatic/presymptomatic patients, enables us to assess disease progression and to determine treatment effectiveness.

LOPD should be followed up by a multidisciplinary team at centres with experience managing the disease.[23] Patients with respiratory involvement should be followed up at pulmonology consultations within specialised multidisciplinary units.

Symptomatic patients should be followed up on a weekly basis. The recommended tests include respiratory function assessment, motor function assessment, and nutritional status.[14,23] Asymptomatic patients with LOPD should be evaluated at least once per year to enable early detection of the onset of signs or symptoms of the disease, should these appear.

Table 3 Recommended tests for patient follow-up.

Essential tests	Other recommended tests
[•]MRC muscle strength test • 6MWT • R-PAct • Respiratory function testing	[•]NSAD • 10-Metre Walk Test • Timed 4 Stair Climb test • Timed Up and Go test

6MWT: 6-Minute Walk Test; MRC: Medical Research Council; NSAD: North Star Assessment for Limb-Girdle Type Muscular Dystrophies; R-PAct: Rasch-built Pompe-specific Activity.

Follow-up tests

Patient follow-up should include testing of muscle strength, motor function, and respiratory function, as well as patient perceptions (Table 3). Different scales are available to determine these parameters.

The Medical Research Council (MRC) scale is used to measure muscle strength. This scale enables the measurement of the strength of different muscle groups on a scale from 0 (no movement) to 5 (normal strength).[23,53]

The 6MWT is a timed test that is typically used in clinical trials. This test measures the distance that patients are able to walk in 6 minute on a hard, flat surface.[23,54]

The Rasch-built Pompe-specific Activity (R-PAct) scale is recommended for evaluating the impact of the disease on quality of life. The scale consists of an 18-item questionnaire that evaluates the patient's degree of autonomy in personal and social activities of daily living, and is able to detect limitations in the performance of activities and restrictions in social participation, as well as clinically significant changes over time, in patients with Pompe disease, across the spectrum of the disease.[23,55]

Another test that may be considered is the North Star Assessment for Limb-Girdle Type Muscular Dystrophies (NSAD), which was specifically designed to evaluate changes in gait function in patients with dysferlin-deficient muscular dystrophy,[56] and is used in adult patients. The NSAD scale has been validated for limb-girdle dystrophies and several studies currently underway are validating it in Pompe disease.[57] Other timed tests such as the 10-Metre Walk Test, Timed 4 Stair Climb test, and Timed Up and Go test may also be used.[23,35]

Levels of urinary glucose tetrasaccharide (Glc4) are elevated in patients with Pompe disease. Studies suggest that Glc4 levels are correlated with the age of symptom onset and disease phenotype.[58] However, this finding is not specific to Pompe disease (elevated Glc4 levels are also present in urinary tract infections, acute pancreatitis, muscle trauma, and some cancers[58]), and patients with LOPD may present normal levels in early stages of the disease.[20]

Limited data are available on the value of Glc4 as a biomarker of disease severity or treatment response in patients with LOPD.

Follow-up of patients with respiratory involvement

Respiratory function testing should be performed every 6-8 months, both in ventilated and in non-ventilated patients, to ensure adequate follow-up of disease progression and to determine the need for ventilation or to increase the hours of ventilation.[25,26]

In non-ventilated patients, night-time oxycapnography should be performed to detect periods of nocturnal hypoventilation.

In ventilated patients, the ventilator's built-in software may also provide data on usage time, tidal volume, respiratory rate, number of respirations activated by the patient, and leaks; this data sheds light on the efficacy of NIMV.[59] Depending on the results, oxycapnography and sleep studies may also be performed (in patients receiving NIMV).[23,35]

Recommendations for the follow-up of late-onset Pompe disease

[•]

- Patient follow-up should involve the following specialties: neurology, paediatric neurology, internal medicine, pulmonology, rehabilitation, and dietetics.
- Asymptomatic patients should be evaluated at least once per year, whereas symptomatic patients should be evaluated at least once every 6 months.
- Particularly relevant scales for patient follow-up include the manual scale for measuring muscle strength, the 6MWT, the R-PAct, and respiratory function assessment; if possible, the NSAD and other timed tests such as the 10-Metre Walk Test, Timed 4 Stair Climb test, and Timed Up and Go test are also recommended.
- Insufficient data are available to recommend Glc4 measurement in the follow-up of LOPD.

Follow-up of patients with respiratory involvement

[•]

- Patients with respiratory involvement should be followed up at pulmonology consultations within specialised multidisciplinary units.
- Patients should be evaluated every 6-8 months by the pulmonology department.
- The recommended tests for the follow-up of patients with respiratory involvement include:

[○]

- ○ in non-ventilated patients: blood gas analysis, FVC, MIP, MEP, SNIP, cough peak flow, and oxycapnography
- ○ in ventilated patients: blood gas analysis, FVC, MIP, MEP, SNIP, cough peak flow, ventilator built-in software data, and, depending on results, oxycapnography and sleep study
- ○ diaphragm ultrasound and MRI as optional tests

End-of-life care of patients with late-onset Pompe disease

LOPD is a progressive disease that can result in considerable functional impairment, with significant dependency in activities of daily living and advanced respiratory failure. In this phase of the disease, treatment aims to manage symptoms to maintain the best possible quality of life and support the patient and their family until the end of life.[52]

To assist in decision-making regarding end-of-life care, it is advisable for the patient to prepare an advance directives document specifying their decisions about the care and treatments they wish to receive or not to receive when they are no longer able to express their wishes. The 2012 guidelines of the Spanish Society of Pulmonology and Thoracic Surgery offer recommendations on the management of patients with neuromuscular disease at the end of life.[26]

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