Eur J Transl Myol 31 (2): 9798, 2021 doi: 10.4081/ejtm.2021.9798

Exercise, nutrition and enzyme replacement therapy are efficacious in adult Pompe patients: report from EPOC Consortium

Corrado Angelini

Neuromuscular Laboratory, Department of Neurosciences, University of Padova, Padova, Italy

Abstract

Pompe Disease, also known as glycogenosis type 2, is due to deficiency in lysosomal alpha-glucosidase, a lysosomal hydrolase, which presents infantile and late onset subtypes (LOPD). The myopathy in LOPD can be reversed by Enzyme Replacement Therapy (ERT), but might benefit from a concomitant low carbohydrate - high protein diet and aerobic exercise treatment. From 65 Late onset Pompe cases, we were able to obtain in 58 a self-reported evaluation, most of them gave a positive efficacy evaluation of Enzyme Replacement Therapy and they were classified by a self-administered scale as Responders or non-Responders. A cooperative study of a clinical group on LOPD monitored age, sex, BMI, Gardner-Medwin-Walton scale and six minute walking test (6MWT). The only clinical parameters that were significantly associated with a Responder category were the pre-ERT walking distance ($p<0.035$) and the use of regular diet, exercise or both ($p<0.029$). The present study shows that in LOPD this condition can be treated by ERT, but also benefits from concomitant diet and aerobic exercise therapy.

Key Words: Glycogenosis type 2; enzyme replacement therapy; exercise; nutrition.

Eur J Transl Myol 31 (2): 9798, 2021 doi: 10.4081/ejtm.2021.9798

Since 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase has been approved for the treatment of Pompe disease. Studies in neonates showing improved survival were the key fact for market approval.[1,2] Since then several studies in children and adults have shown effects of ERT on walking distance, pulmonary function, muscle strength/function and also on survival.[3–5] However, results also suggest that there is a large variation in the effects of treatment in these patients. The question to be addressed is the possible efficacy of concomitant exercise and nutrition in late-onset Pompe (LOPD), thus the present study documents a Responder (R) and non-Responder (N) status based on patient derived outcomes. With an incidence of approximately 1:40.000 to 1:200.000 births, research progress on this rare disease is slow, hampered by the difficulty to obtain sufficient patient numbers. For example, very little is known about which factors explain the variability in the response to ERT treatment that is observed both in children and adults. Also, guidance on monitoring and treating these patients is relatively scarce. There are currently no internationally accepted guidelines for the ERT treatment of older children and adults with Pompe disease, although national guidelines have been published for several European and non-European countries.[6–10] Finally, development of expert consortia to provide advice and leadership is described.

Formation of the European Pompe Consortium (EPOC) and report of the 5th EPOC meeting

The organization of the network with a steering board group, one representative for each country, and other members, was discussed at the European Neuromuscular Center (ENMC) meeting in 2014. It was agreed by the organizers to propose a formal governance structure for the network. This was incorporated in a final consortium agreement, outlining the structure and rules of the network. Combining clinical, biological and genetic data from different European countries might generate a sufficiently large dataset to allow research into prognostic factors to progress. Furthermore, the joint experience of experts who monitor and treat relatively large numbers of patients with Pompe disease would create a platform to develop recommendations on monitoring and treating patients. Finally, the shared knowledge and experience makes it an ideal organization to provide advice and knowledge to health authorities and policy makers. A consensus about start /stop criteria that were developed by different centers and initiated the EPOC work.[11] The EPOC group has met regularly and here are reported data presented and discussed on ERT treatment at the 5th EPOC meeting in Hamburg in February 2020, organized by Zoltan Lukacs and Benedikt Scoser, at this meeting the participation was limited by the Covid-19 pandemic restrictions.

Eur J Transl Myol 31 (2): 9798, 2021 doi: 10.4081/ejtm.2021.9798

Fig 1. *Participants to 5th EPOC 2020, Erika House on 29 February, Universitatsklinikum, Hamburg-Eppendorf, from left: Thomas Hundsberger, St Gallen, Switzerland; George Papadimas, Athens, Greece; Corrado Angelini, Venice, Italy; Jordi Diaz-Manera, Barcelona, Spain; Stefan Hinze, Munich, Gemany; Benedikt Schoser, Munich, Germany; Peter Meinke, Munich, Germany; Robin Lachmann, London, UK; James Davison, London, UK; Mark Roberts, Manchester, UK.*

The fifth EPOC consortium started on February, 28, 2020 and ended on February 29 at the Erika House, an historical nurse House of Hamburg-Eppendorf Hospital (Figure 1). There was a welcome-introduction from Zoltan Lukas, which gave an overview of Pompe screening status, its world-wide use, its problems, the outlooks and new developments. This was followed by discussion on different methodologies and recommendation for a more widespread use. Simon Heales reviewed the use of urinary tetrasaccaride (Hex4/Glc 4) in his experience in diagnosis and follow-up of Pompe children used at Great Ormon Street Hospital (GOSH), as an efficient support to enzyme analysis that usually is done with acarbose inhibition. Vacuolated lymphocytes represent a good disease hallmark, as well as Hex4/Glc4 are useful diagnostic prognostic biomarkers of Pompe disease. Dr Mark Roberts discussed advances in treatment and possible gene therapy application in these patients. James Davison presented his experience with low dose ERT (20 mg/every week) in children, promising for heart treatment. In his series of 33 infants treated at GOSH: 14 were alive, 12 deceased, 5 children none treated. Discussion of data presented followed and continued at a dinner at Dorint Hotel. On February 29, 2020 Benedikt Schoser introduced the second session, while Zoltan Lukacs was hospitalized for a Covid-19 infection. Dr Jordi Manera Diaz discussed the role of muscle imaging detecting fat and connective tissue infiltration during ERT, while Stefan Hinze presented experimental data on Pompe myoblasts. This was followed by a presentation by Corrado Angelini on ERT treatment results and effect of exercise and nutrition as concomitant supportive therapy to ERT. Jon Muir of International Pompe Association presented the patient prospective after several years of various ERT regimens and opinions about screening and diagnosis options. He underlined future public initiative such as an International Pompe day and status of the art in collaboration, since participants collaborated describing which assessments and progresses obtained for Pompe patients and whatever research activity were applied in the participants' center and/or clinic. Through discussion between all participants, consensus was reached on all topics. Because the assessments used and criteria applied may differ between infants, children and adults, this meeting focused on reaching consensus on several research and clinical topics relevant for adult and children patients. The presentation on the effect of concomitant effect of nutrition and exercise to ERT done by Corrado Angelini on behalf of Italian Pompe group follows below.

Exercise and nutrition in late onset Pompe disease

This report presents the results of the Italian LOPD study group on 65 patients. The investigation aimed to improve response to ERT in adult patients, assessing if the prescription of a regular diet and exercise proved to be beneficial and should be included in recommendations.

Materials and Methods

Patients

Patients were enrolled by several Italian Centres: the Coordinator Centre for Pompe analyzed the data by non-parametric Mann-Whitney and Pearson's chi-squared tests and studied correlations. It was agreed that in order to start treatment a patient needs to be symptomatic. Asymptomatic patients should be closely monitored. Severely affected patients can also start treatment, as long as they have some remaining muscle function. After starting treatment a patient enters a two-year trial period, in which he/she is being evaluated using the clinical outcome measures further described. In principle, treatment will be discontinued if during the two-year trial period there is no sign of stabilization or improvement. However, if the patient deteriorates after stopping treatment, restarting treatment can be considered. The main inclusion criteria were: age ≥ 18 years; diagnosis of LOPD confirmed by enzymatic test and/or genetic analysis; regular ERT for at least 2 years. Main exclusion criteria were: presence of significant cardiovascular diseases (assessed by electrocardiogram or echocardiography); wheelchair bound patients.

Outcome dataset for adult patients

According to the EPOC study the results of the different outcome measures were used, but also indicated by a minimal dataset.
This was discussed for each of the different clinical domains affected in adult patients (i.e. skeletal muscle strength and function).

Muscle function: 6 minute walk test, Gardner-Medwin-Walton (GMW)

The 6 minute walk test (6MWT) and GMW were selected to assess muscle function. The 6MWT provides information on endurance as well as walking speed.[12] A major reason to include the 6MWT is that it has been used as a major clinical outcome measure in all clinical trials of adults, and GMW scale as monitoring tool used in many centres, allowing for long-term follow-up and comparability. The grade of GMW scale was obtained for each patient as follow:

Grade 0 = hyperCKemia, all activities normal;
Grade 1 = normal gait, unable to run freely, myalgia;
Grade 2 = incapacity to walk on tiptoes, waddling gait;
Grade 3 = evident muscular weakness, steppage and climbing stairs with banister;
Grade 4 = difficulty to rise from the floor, Gowers' sign;
Grade 5 = incapacity to rise from the floor;
Grade 6 = incapacity to climb stairs;
Grade 7 = incapacity to rise, from a chair;
Grade 8 = unable to walk unassisted;
Grade 9 = unable to eat unassisted.

The GSGC scale provides a time quantitative and scored measurement of four main motor performances:[12]

G: gait (walk 10 meters)
S: stairs (climb 4 steps)
G: Gowers' maneuver (raise from the floor)
C: chair (rise from a chair).

It was agreed that in order to start treatment a patient needs to be symptomatic. Severely affected patients can also start treatment, as long as they have some remaining muscle function, after a patient enters a two-year trial period, in which he/she is being evaluated using the clinical outcome measures described , treatment will be discontinued if during the two-year trial period there is no sign of stabilization or improvement. However, if the patient deteriorates after stopping treatment, restarting treatment can be considered.

Muscle strength

Manual muscle testing using the Medical Research Council (MRC) grading scale was selected to assess muscle strength. To ensure these data are consistent, a scale ranging from 0 to five without +/– notification should be used. Muscle groups to include are (left and right side if applicable): neck extensors, neck flexors, shoulder abductors, elbow flexors, elbow extensors, hip flexors, hip extensors, hip abductors, knee flexors, knee extensors. Excluded muscle groups were the shoulder adductors, arm extra-rotators and endo-rotators muscle groups, since these are relatively difficult to measure and to standardize, and the strength of these muscles is usually reflected by that of the arm abductors.

Pulmonary function:

Forced vital capacity (FVC) in sitting and supine position were included to assess pulmonary function. It is important to measure FVC in both sitting and supine position, because diaphragmatic weakness is common in Pompe disease

Patient reported outcomes

For ERT treatment as a new item of response in this study was used a disease-specific activity scale, here presented (Figure 2). This brief questionnaire consists of 5 items and was developed to measure the change of function evaluated by late-onset Pompe patients' in their ability to carry out daily life activities and functions similar to what described in GSGC scale. This scale was validated in 40 patients in a previous study showing improvement of functions.[13]

Nutrition and exercise information collected in the study

To allow objective and self-reported dataset to be used for analysis of the effects of treatment and prognostic factors, it is important to collect information on treatment

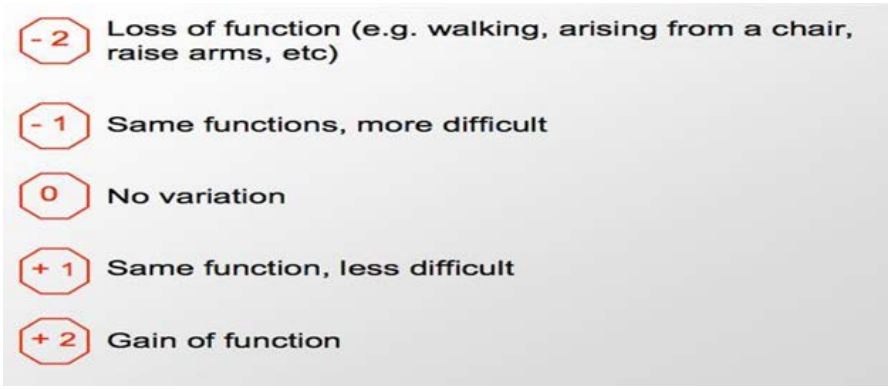

Fig 2. *Patient self-administered questionnaire to evaluate ERT efficacy*

(has the patient regularly received medication for Pompe disease, and if so, which treatment and since/until when) as well as type of exercise and nutrition status (including daily diet and type of diet) as supportive therapy. A study published in the pre-ERT era, dealing with LOPD patients on high-protein diets, reported that only 25% of patients showed improvement in muscle or respiratory function. However, the compliance to the diet was very poor. The authors attributed the problems of compliance to the large amount of prescribed proteins and to the associated perceived risk of weight gain.[12] The LOPD patients interviewed personalized their own diet and exercise regimen. The lack of studies on nutritional interventions in LOPD patients receiving chronic ERT was only recently partially filled by a study in 11 patients evaluating their VO2 max.[14]

Results

In 65 LOPD cases, followed by the Italian Group, coordinated by three physicians (C. Angelini, A. Toscano, T. Mongini) most of the patients gave a positive efficacy evaluation of ERT and they were classified by the self-administered scale as Responders (R) or non-Responders (N). Of the 58 LOPD patients recruited (Figure 3), the majority (35 patients), self-reported a positive improvement in their function, 11 had a two grades gain of function and 24 performed the same function more easily (such as walking, Gowers' maneuver, climbing stairs). 18 patients reported no variation in their motor functions while 4 reported less ability in their functions and only one reported loss of function(s). We therefore divided our series in 35 R = Responders including in this category patients that were stable while 23 were classified in the Non-responder = N category. We studied in Responders and Non-responders average and standard deviation, clinical efficacy by nonparametric Mann-Whitney test making comparisons to the following variables: age at onset of ERT, the initial Gardner-Medwin-Walton grade, BMI, duration of ERT treatment that resulted not significant. This was analyzed for each variable but the only significant parameter was a better performance in meter length walked in 6MWT at

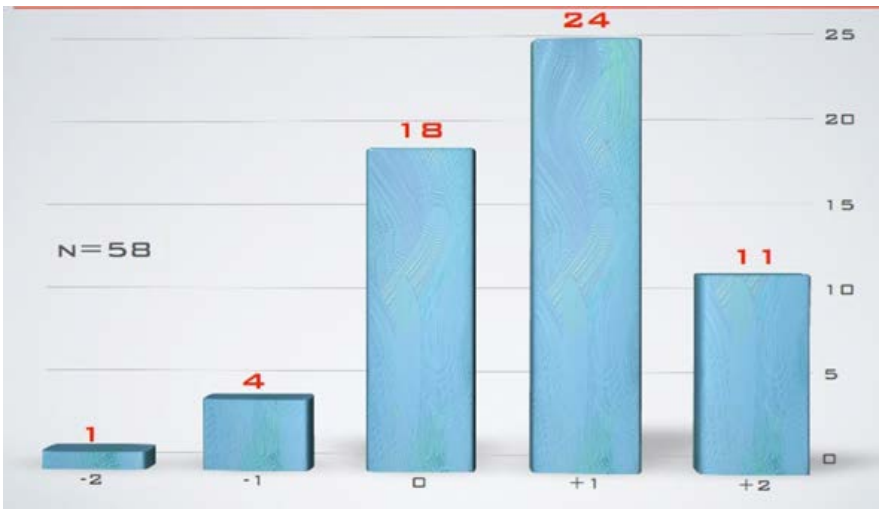

Fig. 3*.Results in 58 LOPD of ERT efficacy evaluation*

Table 1. *Parameters of Clinical efficacy in Non-responders (N) and Responders (R) patients*

	Average		Patient number		SD		P Mann-Whitney
	N	**R**	**N**	**R**	**N**	**R**	
Age (yrs)	46.04	45.11	25	36	10.81	13.56	N.S.
Disease duration (yrs) at T0	17.20	14.42	25	36	9.57	9.10	N.S.
BMI at T0	25.11	22.70	13	22	5.97	5.37	N.S.
GMW at T0	3.91	3.22	22	23	2.47	1.98	N.S.
6 MWT at T0	238.27	344.40	15	25	159.40	112.10	**0.035**
FVC at T0	60.36	67.80	23	33	28.30	19.83	N.S.

Gender	**Patient number (%)**		**Pearson Chi square**
	N	R	
M	13 (52%)	12 (34%)	N.S.
F	12 (48%)	23 (66%)	N.S.
Supportive therapies	**Patient number (%)**		**Pearson Chi square**
	N	R	
Diet and physical activities	5 (20%)	17 (47%)	**0.029**
Only diet, only physical activities, none	20 (80%)	19 (53%)	

SD, standard deviation; P Mann-Whitney and Pearson Chi square: N.S., non-significant

onset before ERT i.e. 344 meters in Responders versus 238 meters in Non-responders ($p<0.035$) (Table 1).

By the self-evaluation questionnaire the patients that gave a positive efficacy evaluation of ERT were 35 cases, while 18 reported stable conditions, they were classified by the self-administered scale in Non-responders (N), the gender in these groups was equally represented.

Then supportive therapies were further studied by the Pearson's chi-squared test that showed that a clinical parameter significantly associated with a Responder category was the use of supportive therapies such as regular diet or exercise or both. Of patients following both diet and exercise 47% were in R category. Those following only either regular diet or exercise in 53% resulted in the R category ($p < 0.029$).

Discussion

ERT has been studied in numerous European series of patients.[5,15] To allow to better monitor ERT a choice of responder patients would be required, this was the main result in our study, in order to further analyze the effects of treatment and prognostic factors, it is important to collect information on treatment (has the patient regularly received medication for Pompe disease, and if so, which treatment and since/until when) as well as the concomitant follow-up for regular exercise and nutrition status (including daily diet and type of diet) that might result in a positive recommendation for these supportive therapy in patients with a confirmed diagnosis. Similarly, the European Pompe Consortium recommends initiating ERT in symptomatic patients who agree to regular treatment and monitoring, have residual skeletal and respiratory muscle function, and do not have another life-threatening illness in an advanced stage.[11] However, to better identify the predictors of the therapeutic response, it is crucial to continue to collect data on cohorts of patients with LOPD. In LOPD patients receiving chronic care a protein rich diet or exercise was tried by Slonim et al.[12] but it could be linked to limited results because of the difficulty of guaranteeing compliance to high-protein diets, as a consequence of the lower palatability of many high-protein foods compared to those with high carbohydrate content, or of the higher satiety power of proteins, which may lead to a reduction in food. The Slonim study published in the pre-ERT era, dealing with LOPD patients on high-protein diets, reported that only 25% of patients showed improvement in muscle or respiratory function. There is only one study on nutritional interventions in LOPD patients receiving chronic ERT.[14] The current standard of care for Pompe

disease is the administration of enzyme replacement therapy (ERT),[16] while exercise and nutrition should be considered as complementary strategies rather than "treatments" per se. Nutritional assessment is important in patients with motor disability because the relative lack of exercise limits energy expenditure and thus the total amount of energy must be reduced to avoid obesity. A lower total energy intake often leads to lower protein and micronutrient intake. Consequently, ensuring that LOPD patients are tested for and replaced for deficiencies (protein, vitamin D, etc.) is an important aspect of care. Furthermore, given the role of autophagy in the pathophysiology of LOPD, and the fact that exercise induces autophagy,[17] it is important that strategies such as diet and exercise are used in combination to ERT.

In conclusion, the available data show that pre-ERT performance during 6MWT is a significant factor associated with Responder category. In LOPD patients there was non-significant improvement of muscle strength,[18] while respiratory status was maintained.[19]

More prospective data would be needed to prove the effect of supportive therapies, but the present results show the importance of a dietary and exercise protocol concomitant to ERT.

Furthermore we propose that in future the use of a mobile App may implement controls on such benefits for patients.[20]

List of acronyms

ERT - Enzyme Replacement Therapy
EPOC - European Pompe Consortium
ENMC - European Neuromuscular Center
LOPD - Late Onset Pompe Disease
BMI - Body Mass Index
6MWT - Six minute walk test
FVC - Forced Vital Capacity
GMW - Gardner-Medwin-Walton scale
GSGC - Gait, Stairs, Gowers, Chair scale
R - Responder
N - Non-Responder

Author contributions

This is a One-Author paper.

Acknowledgments

Funding

This workshop was made possible with the financial support of the European Neuromuscular Centre (ENMC) and its main sponsors: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Telethon Foundation (Italy), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzeland) Muscular Dystrophy Campaign (UK).

Conflict of Interest

The author declares no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Corrado Angelini, Neuromuscular Laboratory, Department of Neurosciences, University of Padova, Padova, Italy
ORCID iD: 0000-0002-9554-8794
E-mail: corrado.angelini@unipd.it

References

1. Van den Hout JM, Kamphoven JH, Winkel LP, Arts WF, De Klerk JB, Loonen MC, Vulto AG, Cromme-Dijkhuis A, Weisglas-Kuperus N, Hop W, Van Hirtum H, Van Diggelen OP, Boer M, Kroos MA, Van Doorn PA, Van der Voort E, Sibbles B, Van Corven EJ, Brakenhoff JP, Van Hove J, Smeitink JA, de Jong G, Reuser AJ, Van der Ploeg AT. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. Pediatrics. 2004 May;113(5):e448-57. doi: 10.1542/peds.113.5.e448.
2. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, Leslie N, Levine J, Spencer C, McDonald M, Li J, Dumontier J, Halberthal M, Chien YH, Hopkin R, Vijayaraghavan S, Gruskin D, Bartholomew D, van der Ploeg A, Clancy JP, Parini R, Morin G, Beck M, De la Gastine GS, Jokic M, Thurberg B, Richards S, Bali D, Davison M, Worden MA, Chen YT, Wraith JE. Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. Neurology. 2007 Jan 9;68(2):99-109. doi: 10.1212/01.wnl.0000251268.41188.04. Epub 2006 Dec 6. Erratum in: Neurology. 2008 Nov 18;71(21):1748.
3. de Vries JM, van der Beek NA, Hop WC, Karstens FP, Wokke JH, de Visser M, van Engelen BG, Kuks JB, van der Kooi AJ, Notermans NC, Faber CG, Verschuuren JJ, Kruijshaar ME, Reuser AJ, van Doorn PA, van der Ploeg AT. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. Orphanet J Rare Dis. 2012 Sep 26;7:73. doi: 10.1186/1750-1172-7-73.
4. Güngör D, Kruijshaar ME, Plug I, D'Agostino RB, Hagemans ML, van Doorn PA, Reuser AJ, van der Ploeg AT. Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study. Orphanet J Rare Dis. 2013 Mar 27;8:49. doi: 10.1186/1750-1172-8-49.
5. Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol. 2013 Apr;260(4):951-9.

doi: 10.1007/s00415-012-6636-x. Epub 2012 Aug 28.

6. Barba-Romero MA, Barrot E, Bautista-Lorite J, Gutierrez-Rivas E, Illa I, Jimenez LM, Ley-Martos M, Lopez de Munain A, Pardo J, Pascual-Pascual SI, Perez-Lopez J, Solera J, Vilchez-Padilla JJ. Clinical guidelines for late-onset Pompe disease. Rev Neurol. 2012 Apr 16;54(8):497-507. English, Spanish.
7. Cupler EJ, Berger KI, Leshner RT, Wolfe GI, Han JJ, Barohn RJ, Kissel JT; AANEM Consensus Committee on Late-onset Pompe Disease. Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve. 2012 Mar;45(3):319-33. doi: 10.1002/mus.22329. Epub 2011 Dec 15.
8. Hundsberger T, Rohrbach M, Kern L, Rösler KM. Swiss national guideline for reimbursement of enzyme replacement therapy in late-onset Pompe disease. J Neurol. 2013 Sep;260(9):2279-85. doi: 10.1007/s00415-013-6980-5. Epub 2013 Jun 8.
9. Llerena JC Jr, Horovitz DM, Marie SK, Porta G, Giugliani R, Rojas MV, Martins AM; Brazilian Network for Studies in Pompe Disease (ReBrPOM). The Brazilian consensus on the management of Pompe disease. J Pediatr. 2009 Oct;155(4 Suppl):S47-56. doi: 10.1016/j.jpeds.2009.07.006.
10. Schüller A, Kornblum C, Deschauer M, Vorgerd M, Schrank B, Mengel E, Lukacs Z, Gläser D, Young P, Plöckinger U, Schoser B. Diagnose und Therapie des Late-onset-Morbus-Pompe [Diagnosis and therapy of late onset Pompe disease]. Nervenarzt. 2013 Dec;84(12):1467-72. German. doi: 10.1007/s00115-013-3947-9.
11. van der Ploeg AT, Kruijshaar ME, Toscano A, Laforêt P, Angelini C, Lachmann RH, Pascual Pascual SI, Roberts M, Rösler K, Stulnig T, van Doorn PA, Van den Bergh PYK, Vissing J, Schoser B; European Pompe Consortium. European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience. Eur J Neurol. 2017 Jun;24(6):768-e31. doi: 10.1111/ene.13285. Epub 2017 May 6.
12 Slonim AE, Bulone L, Goldberg T, Minikes J, Slonim E, Galanko J, Martiniuk F. Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. Muscle Nerve. 2007 Jan;35(1):70-7. doi: 10.1002/mus.20665
13 Angelini C, Semplicini C, Ravaglia S, Moggio M, Comi GP, Musumeci O, Pegoraro E, Tonin P, Filosto M, Servidei S, Morandi L, Crescimanno G, Marrosu G, Siciliano G, Mongini T, Toscano A; Italian Group on GSDII. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. Muscle Nerve. 2012 Jun;45(6):831-4. doi: 10.1002/mus.23340.
14. Sechi A, Zuccarelli L, Grassi B, Frangiamore R, De Amicis R, Marzorati M, Porcelli S, Tullio A, Bacco A, Bertoli S, Dardis A, Biasutti L, Pasanisi MB, Devigili G, Bembi B. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: results of a cross over study. Orphanet J Rare Dis. 2020 Jun 6;15(1):143. doi: 10.1186/s13023-020-01416-6.
15. Angelini C, Semplicini C, Tonin P, Filosto M, Pegoraro E, Sorarù G, Fanin M. Progress in Enzyme Replacement Therapy in Glycogen Storage Disease Type II. Ther Adv Neurol Disord. 2009 May;2(3):143-53. doi: 10.1177/1756285609103324.
16 Angelini C, Semplicini C, Pegoraro E. Clinical follow-up and efficacy evaluation in ERT. Advances in Diagnosis and Management of Glycogenosis II. Nova Science Publishers, Inc. Hauppauge, NY, USA. 2013; pp. 137-144.
17. Angelini C, Nascimbeni AC, Semplicini C. Therapeutic advances in the management of Pompe disease and other metabolic myopathies. Ther Adv Neurol Disord. 2013 Sep;6(5):311-21. doi: 10.1177/1756285613487570.
18. Angelini C, Semplicini C, Ravaglia S, Bembi B, Servidei S, Pegoraro E, Moggio M, Filosto M, Sette E, Crescimanno G, Tonin P, Parini R, Morandi L, Marrosu G, Greco G, Musumeci O, Di Iorio G, Siciliano G, Donati MA, Carubbi F, Ermani M, Mongini T, Toscano A; Italian GSDII Group. Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. J Neurol. 2012 May;259(5):952-8. doi: 10.1007/s00415-011-6293-5. Epub 2011 Nov 12.
19. Vianello A, Semplicini C, Paladini L, Concas A, Ravaglia S, Servidei S, Toscano A, Mongini T, Angelini C, Pegoraro E. Enzyme replacement therapy improves respiratory outcomes in patients with late-onset type II glycogenosis and high ventilator dependency. Lung. 2013 Oct;191(5):537-44. doi: 10.1007/s00408-013-9489-x. Epub 2013 Jul 10.
20. Ricci G, Baldanzi S, Seidita F, Proietti C, Carlini F, Peviani S, Antonini G, Vianello A, Siciliano G; Italian GSD II group. A mobile app for patients with Pompe disease and its possible clinical applications. Neuromuscul Disord. 2018 Jun;28(6):471-475. doi: 10.1016/j.nmd.2018.03.005. Epub 2018 Mar 12.

Submitted: April 04, 2021
Revision received: April 21, 2021
Accepted for publication: April 21, 2021