Effects and health economic aspects of enzyme therapy in children and adults with Pompe disease. Long-term follow-up of patients receiving commercially available Myozyme

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This study has been transitioned to CTIS with ID 2024-518269-92-00 check the CTIS register for the current data. The objective of the study is to gather more information about the long-term effect of enzyme therapy in patients with Pompe disease...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON47930

Source
ToetsingOnline

Brief title
not applicable

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Muscle disorders

Synonym
acid maltase deficiency, glycogenosis type II

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: CVZ (via ZonMW);TI Pharma (deelonderzoek neonatale screening)

Intervention

Keyword: Enzyme therapy (Myozyme), Health economic aspects, Long-term follow-up, Pompe disease

Outcome measures

Primary outcome

- Survival

- Muscle strength and function

- Motor and mental outcome

- Pulmonary function

- Cardiac hypertrophy and function

- Hearing loss

- Disease specific symptoms, handicap, quality of life and fatigue

- Muscle mass and regeneration

- Costs

- Enzyme activity in dried blood spots

- Health damage at diagnosis

- Attitude health care workers towards newborn screening for

Pompe disease

- Aortic stifness, pulse wave velocity, distensibility and

intima-media thickness

- Function and strength of the diaphragm

- Thickness of the diaphragm

- Modifying factors

- IQ

- neuropsychological function tests

- Brain MRI

- Muscle MRI/ultrasound

- EMG findings

- Prevalence of cardiovascular morbidity

- Risk factors for cardiovascular morbidity

Secondary outcome

Core stability

Pulmonary abnormalities

Body composition

Overall fitness

Study description

Background summary

Pompe disease (glycogen storage disease type II) is a genetic, lysosomal storage disorder with a frequency of 1 in 40.000 newborns. The disease is caused by deficiency of alpha-glucosidase, a lysosomal hydrolase involved in the degradation of glycogen. This deficiency causes accumulation of glycogen in many tissues, like cardiac and skeletal muscle and liver tissue. Patients with the classic infantile form of Pompe disease have severe cardiorespiratory problems and motor developmental delay. These children usually die within the first year of life. Patients with the non-classic form of the disease can present at any age and there is a spectrum in severity of disease.

Until recently, no therapy was available for patients with Pompe disease. In 2006 treatment with Myozyme (alglucosidase alfa; enzyme therapy) was registered for long term treatment of all patients with Pompe disease (both children and adults). However, information about the effect of enzyme therapy is limited, especially in older children and adults. Further research is essential, especially to determine the long-term effects of enzyme therapy.

Therapy for the classic infantile form of Pompe's disease is most effective if started as soon as possible after diagnosis. Currently, the average diagnostic delay is 5,3 months. Early diagnosis is essential for better outcome in survival, respiratory, cardiac and muscle function. An obvious way to reduce this diagnostic delay in Pompe's disease would be early detection with universal newborn screening. Alternative treatment regimens, for example a different dose or the use of immunomodulation, may also further improve treatment outcomes in this patient group is.

Exercise training possibly further improves muscle strength and muscle function. Exercise training programs improve oxidative capacity and muscle function in other myopathies. Existing studies on exercise training programs in patients with Pompe disease are not performed systematically or are performed in small groups of patients. Therefore exercise training is not a standardized treatment for patients with Pompe disease. A recent inventarisation in 51 adult patients showed that there patients would like to combine a standardized exercise trainings program and/or physical therapy program with their enzyme replacement therapy.
As previously shown, exercise therapy improves endurance, muscle strength, muscle function and core stability. However, little is known about the long term effects of exercise therapy in Pompe patients. We would like to know whether patients benefit from exercise therapy in the long term, thus whether their physical functioning and fitness is better with exercise in addition to enzyme therapy.

Patient with Pompe disease might have an increased aortic stiffness due to accumulation of glycogen in the vessel wall. This could be an independent risk factor of cardiovascular accidents.

Since the start of treatment with enzyme replacement therapy muscle strenght and pulmonary function in sitting position stabilize or improve. The effects on pulmonary function in supine position are less pronounced; in 1/3 of the patients this parameter decreases despite treatment. The decrease in pulmonary function in supine position is possibly due to weakness of the diaphragm. With MRI in combination with spirometry we want to obtain insight into the function and strength of the diaphragm and pulmonary abnormalities. Moreover we want to investigate the effects of enzyme replacement therapy on the diaphragm.

In non-classic Pompe disease, which may present at any age, muscular weakness is the predominant symptom. However, the clinical phenotype is very variable.

In a substantial number of these patients features of Pompe disease which are less familiair to clinicians are present, such as bulbar weakness, scapular winging or ptosis. In Facioscapulohumeral dystrophy (FSHD), scapular winging and facial weakness are the key symptoms. Recently, a second gene related to FSHD has been identified as:SMCHD1(FSHD2) . Recent family studies show that SMCHD1 can co-segregate in patients with FSHD1 but also in patients with other hereditary muscular dystrophies with similar phenotype. SMCHD1 might therefore play a role as an epigenetic regulator in muscular dystrophies.

During long-term treatment with enzyme replacement therapy we notice that new features emerge in Pompe disease. We found hampering of cognitive development or even neurological deterioration in treated patients with classic infantile Pompe disease. Also we noticed the development of distal weakness in both classic infantile and late onset Pompe disease. Both can be driven by the involvement of the central and peripheral nervous system.

Previous research showed increased aortic stiffness and blood pressure in adult Pompe patients compared to controls. These are independent risk factors for cardiovascular disease and may lead to more cardiovascular morbidity in Pompe patients.

Study objective

This study has been transitioned to CTIS with ID 2024-518269-92-00 check the CTIS register for the current data.

The objective of the study is to gather more information about the long-term effect of enzyme therapy in patients with Pompe disease with a different severity of disease. The goal is also to set guideline for start and stop of treatment and to evaluate health economic aspects. Furthermore, it is important to find an optimal dosing regimen.
We will study whether newborn screening for Pompe disease in The Netherlands is possible and desirable/ advisable.
Furthermore, the effectiveness and safety of a standardized exercise trainings program next to enzyme replacement will be studied.
The frequency and characterization of pain in adult patients with Pompe disease will be studied.
Aortic stiffness in adult patients with Pompe disease will be studied.
Study the function and strength of the diaphragm and effects of enzyme replacement therapy.
Modifying factors in Pompe disease will be investigated.
To characterize the occurrence and the extent of clinical and radiological features of CNS involvement in ERT-*treated classic infantile Pompe patients in different age groups, and to investigate its course over time. To investigate whether impaired functioning of anterior horn cells, peripheral nerves, or neuromuscular junction contribute to the development of distal muscle weakness of the limbs.

To investigate the prevalence of cardiovascular morbidity and cardiovascular risk factors in adult Pompe patients.

Study design

This study is a therapeutic intervention study with a registered product.
Patients are followed for at least 3 years by general/neurological examination, combined with examination of muscle strength and function, pulmonary function, cardiac function and hearing.
For the substudy on newborn screening, the bloodspots of patients with Pompe's disease, parents of patients with Pompe's disease and anonymous Guthrie cards from the RIVM (National Institute for Public Health and the Environment) will be analysed with a fluorimetric method and tandem mass spectometry. Health damage at diagnosis will be evaluated using information from medical files and questionnaires. Semi-structured interviews will assess the attitude of health care workers towards the possible implementation of Pompe disease to the national newborn screening project.
For the substudy on exercise training patient will be placed randomized in two groups. Group 1 will start with the exercise trainings program and will train for 3 months. The last 3 months of the study they will not train in order to study the effects of "detraining". Group 2 will not train for the first 3 months and therefore serve as controls for group 1. They will train the last 3 months of this substudy. Patients are followed by muscle strength, muscle function and muscle architecture, body composition, endurance and quality of life.
The substudy for pain in Pompe dsiease is a cross-sectional, observational study. Patients 18 years and older will be asked to complete once a subset of questionnaires on pain.
The substudy for aortic stiffness in Pompe disease is a case control study. Ultrasound is a non-invasive way to measure pulse wave velocity and distensibility of the a. carotis and a. femoralis. It's the golden standard for measuring the aortic stiffness.
The substudy on the function of the diaphragm is a case control study. MRI in combination with spirometry is a non-invasive way to measure this function and the strength of the diaphragm. To investigate changes over time, we will repeat the MRI scan after one year. Secondly we aim to make an ultrasound of the diaphragm to investigate whether this correlates with MRI-findings and lung function.
The substudy on modifying factors in Pompe disease is a cross-sectional study. Three tubes of blood will be taken just before start of treatment with enzyme replacement therapie, so patients don't need an extra vena punction.
The international study on treatment regimens is a retrospective study on data available in the patient files.
The study on the emerging new features in Pompe disease is a prospectively observational study in which patients will be followed up by neuropsychological tests, MRI's of the brain and nerve and muscle ultrasounds. A muscle biopsy, EMG, SSEP, VEP, ORG and OCT and a MRI of the myelum and lower extremities will

be performed once. The muscle MRI of the lower extremities and a one time MRI of the brain will be conducted at the LUMC.
The substudy on cardiovascular morbidity is a case-control study. Length, weight, hip circumference and waist circumference will be measured. Participants will be asked to fill in a questionnaire regarding cardiovascular risk factors. 30-minute blood pressure measurement, blood analysis and urinalysis and an EKG will be performed.
The substudy on long term effects of exercise therapy is a cross-sectional study. Patients included in the previous exercise study
will be included again. Patients who didn*t follow the exercise program at the time will be included as controls. They will be matched by gender, age and also disease progression at the time of the previous exercise therapy. Data of the standard outpatient clinic assessments will be collected. These assessments contain vital parameters, height, weight, standard blood and urine tests, pulmonary function, six minutes walking test, muscle strength measured manually and by HHD (hand held dynamometry), muscle function measured with GMFM (gross motor function measure) and timed tests. Patients will be asked to visit the outpatient clinic for an extra day. This is necessary to perform endurance tests by cycle ergometer, to fill in questionnaires about fitness and fatigue and to measure bone density and body composition using a dexa-scan.

Intervention

All patients who participate in the study will receive Myozyme. Myozyme is a registered (orphan)drug for treatment of all patients with Pompe disease. Patients will come once every 2 weeks to the Erasmus MC for their infusions.
Patients participating in the substudy on exercise training will follow a standardized exercise trainings program for 3 months.
Patients participating in the substudy on aortic stiffness will get a non-invasive measurement wih ultrasound of the a. carotis and a. femoralis.
Patients participating in the substudy on function of the diaphragm will get an MRI in combination with spirometry and an ultrasound of the diaphragm.
Of patients participating in the substudy on modifying factors 3 tubes of blood will be taken just before start of treatment with enzyme replacement therapie, so patients don't need an extra vena punction.
Patients participating in the substudy on emerging new features will be studied by the above mentioned examinations.
Patients participating in the substudy on cardiovascular morbidity will be studied by the above mentioned examinations.
Patients participating in the substudy on long term effects of exercise therapy will be studied by the above mentioned mostly standard outpatient clinic examinations.

Study burden and risks

During the study, blood will be drawn and in some patients a skin and muscle

biopsy will be performed. All other study evaluations like general/neurological evaluation, pulmonary function, cardiac function and hearing are considered without risk. Patients will come once every 2 weeks to the hospital for their infusion. All other examinations will be combined with this infusion visit.
For the substudy on newborn screening, blood will be drawn once from the parents of patients with Pompe's disease to prepare blood spots in which enzyme activity will be measured.
Patients participating in the substudy on exercise training have to visit the hospital for additional assessments. Exercise training possibly further damages muscle tissue. Earlier studies on exercise training in patients with Pompe disease have not found any further damage. Furthermore we will monitor muscle damage by biweekly analysis of blood samples (0.5 ml) taken before the start of the enzyme replacement therapy.
There will be no risks for the patients and controls participating in the substudy on aortic stiffness. The ultrasound will take place during a visit when the patients and controls are already at the Erasmus MC.
For the substudy on the function of the diaphragm patients do not have to visit the hospital an extra time. The MRI will be scheduled during one of the regular visits or on the day the patient receives his infusion in the Erasmuc MC. There aren't major risks for the patients. They only could get short-winded during the investigation.
For the substudy on modifying factors patients do not have to visit the hospital an extra time. Three tubes of blood will be taken just before start of treatment with enzyme replacement therapie, so patients don't need an extra vena punction. There aren't additional risks for the patients. Only the already existing risk of the vena punction for administration of ERT.
All patients will have a muscle biopsy and a nerve conduction and needle myography. Children under the age of 7 years will be anesthesized to enable these procedures and the MRI's.
For the sub study on cardiovascular morbidity all investigations will take place during the patient*s regular assessment day. One extra tube of blood will be drawn from patients, there will be no additional venipuncture for patients. Controls will undergo a venipuncture once, three tubes of blood will be drawn.
Patients participating in the substudy on long term effects of exercise therapy will be asked to visit the outpatient clinic one extra day for approximately 6 hours to perform the afore mentioned examinations. This will be asked just once.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients should have a proven diagnosis of Pompe disease, which means that the diagnosis is confirmed by deficiency of a-glucosidase activity in leukocytes or skeletal muscle, or by a documented mutation in the a-glucosidase gene.
2. The patient must have symptoms of Pompe disease being: Signs of skeletal muscle weakness, or decreased pulmonary function (FVC < 80% in sitting position), or Cardiac hypertrophy
3. Parents participating in the substudy on neonatal screening must have been identified as carriers of Pompe disease. The parents have previously been tested positive for carrierschip.
4. Patients participating in the substudy on exercise training should be at least 17 years old and should have been treated with enzyme replacement therapy for at least 1 year.
5. Patients participating in the substudy on pain in Pompe disease should be 18 years or older.
6. Patients participating in the substudy on stiffness of the aorta should be

18 years or older.
7. Patients participating in the substudy on the function of the diaphragm investigated by MRI and spirometry should be 8 years or older. They should be able to lie down in an MRI for 30 minutes and have no contra indications like a pacemaker or other metals in their body.
8. All patients above the age of 18 years old will participate in the substudy about scapular winging.
9. Patients participating in the international study on treatment regimens should be diagnosed before 12 months of age and have hypertrophic cardiomyopathy.
10. All patients with classic infantile Pompe disease will participate in the study on the involvement of the central or peripheral nervous system; a subset of patients with non-classic phenotypes (older children and adults) will participate in this substudy. MRI of brain and muscles will be performed in a subset of 10-15 healthy age matched controls
11. All patients above the age of 18 years old will be asked to participate in the substudy on cardiovascular morbidity.
12. Patients participating in the substudy on the long-term effects of exercise training should have participated in the former exercise study. Patients who might serve as control patient should be at least 17 years old and should have been treated with enzyme replacement therapy for preferably 8 years.

Exclusion criteria

1. Patients who are not likely to benefit from treatment
2. Patients participating in the substudy on exercise training should not be involved in another exercise program
3. Patients participating in the substudy on the function of the diaphragm investigated by MRI and spirometry should not use mechanical ventilation in daytime or have metal objects in their body.
4. Patients and healthy controls, who will undergo MRI of brain and muscles (substudy on the involvement of the central or peripheral nervous system) should not have metal objects in their body.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-06-2007
Enrollment:	152
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Myozyme
Generic name:	alglucosidase alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-07-2007
Application type:	Amendment
Approved WMO Date:	25-11-2009
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22791
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-518269-92-00
EudraCT	EUCTR2007-001375-11-NL
CCMO	NL16769.078.07
Other	not applicable