Natural course, effects of enzyme therapy and health economic aspects in patients with mucopolysaccharidosis type I, II and VI. Long-term folloe-up of untreated patients and patients receiving commercially available Aldurazyme, Elaprase and Naglazyme.

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

Summary

ID

NL-OMON35691

Source
ToetsingOnline

Brief title
Enzyme therapy in patients with MPS type I, II and VI

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Musculoskeletal and connective tissue disorders congenital

Synonym
Hunter syndrome and Maroteaux-Lamy syndrome), lysosomal storage disorders (Hurler syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Enzyme therapy, Health economic aspects, Mucopolysaccharidoses, Natural course

Outcome measures

Primary outcome

- Survival

- Physical endurance

- Joint mobility

- Cardiac size and function

- Pulmonary function, apnoea syndrome and need for respiratory support

- Urine GAG levels

- Size of liver and spleen

- Corneal clouding and eye function

- Morphometry of the face

- Quality of life

- Costs

- Enzyme activity in dried blood spots

Secondary outcome

Not applicable

Study description

Background summary

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders, all caused by the deficiency of a specific enzyme required for the stepwise degradation of glycosaminoglycans (GAGs). The deficiency of one of these enzymes results in accumulation of partially degraded GAG's in the lysosomes of various tissues. For example, in MPS I and II the storage products are dermatan and heparan sulphate; in MPS VI only dermatan sulphate accumulates. The clinical features of the mucopolysaccharidoses involve different organ systems. In all MPS there is a chronic and progressive clinical course leading ultimately to premature death. Characteristic symptoms are coarse facial features, skeletal deformities and an enlargement of the liver and the spleen. Furthermore, hearing, vision and joint range of motion may be impaired and patients may have cardiac and respiratory problems. In the severe forms of MPS I and II mental retardation is also present, while in MPS VI the central nervous system does not seem to be involved. The MPS are rare diseases with an estimated birth prevalence in the Netherlands of 1 in 22.000 for all MPS together.

Until recently, no therapy was available for patients with MPS I, II and VI. Recently enzyme therapy was registered for treatment of these disorders. However, information about the effect of enzyme therapy is limited. Further research is essential to determine the precise effects of enzyme therapy. Furthermore it is necessary to increase the knowledge on the natural course of MPS I, II and VI to measure these effects.

Although the follow-up time and number of treated patients are still limited, it is expected that an earlier
start of treatment will lead to better outcome. Furthermore, for patients with the severe Hurler
phenotype of MPS I hematopoietic stem cell therapy (HSCT) is the treatment of choice. This
treatment should be given before the age of 2 years, but preferably even sooner after birth.
If diagnosis could be moved forward to the first month of life, MPS I-Hurler patients would be
detected long before the critical age for HSCT of 2 years, and both HSCT for Hurler patients
and ERT for the other patient groups could be started sooner. An obvious way to reduce

diagnostic delay for the MPSes would be universal newborn screening.

Study objective

the objective of the current study is to evaluate the safety and efficacy of enzyme therapy in the Dutch population of patients with MPS I, II and VI; to compare this to the natural course of these diseases; to make an inventory of the direct and indirect costs of the MPS and the effects of enzyme therapy on these costs. and to make guidelines to safely install enzyme therapy at home. Finally, we will study whether newborn screening for MPS I, II and VI in The Netherlands is possible.

Study design

This study is a therapeutic intervention study with a registered product. Patients will be followed for at least 3 years (with a maximum duration untill the 2013) by general/neurological examination, combined with additional examination of endurance, pulmonary function, cardiac size and function, size of liver and spleen, joint mobility, vision and hearing, quality of life and mental and social functioning.
For the substudy on newborn screening, the bloodspots of patients with MPS I, II and VI, parents of patients with MPS I, II and VI 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. To study the mental development of patientens with MPS siblings of patients will be assessed once.

Intervention

MPS I patients, participating in the therapeutic part of the study will receive infusions with Aldurazyme, MPS II patient with Elaprase and MPS VI patients with Naglazyme. These medications are registered (orphan)drugs for treatment of MPS I, II and VI. Patients will be treated once a week at the Erasmus Medical Center/ Sophia Children's Hospital.

Study burden and risks

Except for the risks involved with a skin biopsy no specific risks excist. Patients, participating in the therapeutic part of the study, will visit the hospital once every week to receive their treatment. All other examinations will be combined with infusion visits.
For the substudy on newborn screening, blood will be drawn once from the parents of patients with mucopolysaccharidosis type I, II and VI to prepare blood spots in which enzyme activity will be measured. To minimize the burden and time investment the mental development of siblings will be assessed during

a regulare visit of the patient to the hospital.

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. The patient should have a biochemically confirmed deficiency of a-L-iduronidase (MPS I). iduronidate-2-sulfatase (MPS II), or N-acetylgalactosamine-4-sulfatase (MPS VI); or a confirmed mutation in the gene encoding for a-L-iduronidase (MPS I). iduronidate-2-sulfatase (MPS II, or N-acetylgalactosamine-4-sulfatase (MPS VI).
2. The patient has had least one evaluation through which the severity of the disease has been assessed and the urgency of enzyme therapy can be determined.

3. Written informed consent must be obtained from the patient and/or from the patient's parent/guardian if the patient is under 18 years of age.

Exclusion criteria

1. The patient (or parent/legal guardian) is unable or unwilling to comply with the study protocol.
2. The patient has severe neurological involvement as evidenced by:
* total or subtotal absence of cortical activity.
* untreatable seizures
* loss of (almost) all abilities to communicate.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-07-2007
Enrollment:	50
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Aldurazyme
Generic name:	Recombinant human alpha-l-iduronidase
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Elaprase
Generic name:	recombinant human iduronate-2-sulfatase
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Naglazyme
Generic name:	recombinant human arylsulfatase B
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2012
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-001453-26-NL
CCMO	NL16889.078.07