A Proof-of-Concept Study to Explore the Potential Efficacy of Deferiprone in Patients With Pelizaeus-Merzbacher disease (PMD)

Published: 23-06-2022
Last updated: 30-01-2025

This study has been transitioned to CTIS with ID 2024-511968-81-00 check the CTIS register for the current data. Studying the effect of deferiprone on the motor function of patients with Pelizaeus-Merzbacher disease.

Ethical review	Approved WMO
Status	Pending
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON51993

Source
ToetsingOnline

Brief title
Deferiprone as possible treatment for Pelizaeus-Merzbacher disease

Condition

- Congenital and peripartum neurological conditions

Synonym
hypomyelinating leukodystrophy, white matter disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: deferiprone, leukodystrophy, Pelizaeus-Merzbacher disease

Outcome measures

Primary outcome

Primary endpoint

• Gross motor function: Gross Motor Function Measure (GMFM) and Gross Motor

Function Classification System for Metachromatic Leukodystrophy (GMFCS-MLD)

Secondary outcome

Secondary endpoints

• Quantitative brain MRI parameters:

* Diffusion Tensor Imaging (DTI)

* Chemical Shift Imaging (CSI)

* Neurite Orientation Dispersion and Density Imaging (NODDI)

* Myelin Water Fraction Imaging (MWFI)

• Clinical parameters:

* General health and quality of life: Health Utility Index (HUI)

* Hand function: Manual Ability Classification System (MACS)

* Communication: Communication Function Classification System (CFCS)

* Swallowing function: Eating and Drinking Ability Classification System (EDACS)

* Euro-Quality of Life Instrument 5D, 5 levels (EQ-5D-Y, proxy)

* Vineland Adaptive Behavior Scales, 3rd edition (Vineland-3)

• Electrophysiological parameters

* EEG

Exploratory endpoints

• Exploratory search for biomarkers in body fluids.

• Health economic effect (Institute for Medical Technology Assessment (iMTA)

Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire

(iPCQ))

Study description

Background summary

Pelizaeus-Merzbacher disease (PMD) is a devastating brain white matter disorder, caused by mutations in the gene encoding proteolipid protein 1 (PLP1). It is an X-linked disorder, carrier mothers may become symptomatic later in life. In the classic form of the disease, motor handicap is severe: patients are not able to sit without support.

There are more severe and milder forms, depending on the PLP1 mutation. Typically, affected boys develop a pendular nystagmus at the age of several weeks, similar to infants with congenital nystagmus. Shortly thereafter, delayed psychomotor development becomes apparent. These infants show axial hypotonia with difficult head control, titubation, exaggerated tendon reflexes and a combination of ataxia and extrapyramidal features. Nystagmus may improve or even disappear over time. Optic atrophy is common. In classic PMD, patients are unable to walk, and usually unable to sit without support. If they develop active speech, it is difficult to understand because of dysarthria and scanning speech. Learning problems or mental retardation is common, although motor impairment tends to be more pronounced than cognitive disability. In connatal PMD, symptoms are evident shortly after birth and often include congenital stridor, feeding difficulties and profound hypotonia. Development is more impaired than in the classic form, and connatal PMD patients do not learn to talk or sit without support and make very little developmental progress. Microcephaly is common. Transitional PMD is intermediate in severity to the connatal and classic variants. Clinical course in PMD is chronic. Until late childhood or early adolescence, patients may improve and make definite, albeit slow, developmental progress. From this age, however, slow deterioration begins, with insidious progression of neurologic symptoms and slow cognitive

decline. Optic atrophy, if not yet present, develops. While difficult to predict for individual patients, life expectancy is reduced, and depends on severity of neurologic deficits and additional complications. Connatal PMD patients often die within the first decade of life, classic PMD patients in the second or third decade. There is currently no treatment for PMD other than symptomatic treatment. Symptomatic treatment aims at preventing contractures, ensure adequate nutrition (a gastrostomy often becomes necessary) and treating spasticity, among other measures to stabilize general health.

MRI in PMD shows hypomyelination, indicated by diffusely elevated signal white matter signal on T2. There is a severe myelin deficit. Still, when imaged sequentially, PMD patients do show some, albeit a minor progress of myelination, certainly in the first years of life. This progress is greater in children with milder PMD forms. Myelination is then arrested and fails to progress on repeated scans. In older patients, atrophy becomes more prominent.

Located on Xq22.2, PLP1 encodes the proteolipid 1 protein, which constitutes roughly half of all myelin protein. There are different genetic defects affecting PLP1 in PMD patients. Most commonly, the PLP1 gene is duplicated. Missense mutations are less frequent and, depending on the mutation, may lead to even more severe disease. Genotype-phenotype correlations have been established for most PLP1 variants, although some clinical heterogeneity among patients with common genetic alterations makes definitive characterization difficult. Symptoms do not correlate with duplication size, but high copy number (PLP1 triplication) predicts increased clinical severity. Missense mutations are associated with the full spectrum of PLP1-associated disorders. All genetic defects lead to failure of oligodendrocyte lineage maturation, defective myelination and subsequently axonal damage.

There are several mouse models for PMD, among these Jimpy mice, harbouring a severe point mutation in intron 4, causing a putative truncation of Plp1 protein, and animal death by P28. This model is a good representation of human disease, reflecting severe myelin deficit due to early oligodendrocyte death. There is also a mouse model for PLP1 duplication. These mouse models are well characterised.

Recently it has been shown that iron overload may contribute to PMD pathogenesis. This was studied using patient-derived induced pluripotent stem cells (iPSCs) and gene-corrected isogenic cells. PLP1-mutant, iPSC-derived oligodendrocyte precursors (OPCs) developed to the pre-myelinating stage normally, but subsequently underwent apoptosis. Unexpectedly, UPR and ER stress pathways were not activated, and the mutant protein was transported to the cell membrane. Rather, mutant OPCs demonstrated severe lipid oxidative stress, abnormal iron metabolism and sensitivity to extracellular iron. Gene-corrected OPCs, on the other hand, were insensitive to iron. Remarkably, pharmacological iron chelation treatment with iron chelation rescued mutant OPCs in vitro. Systemic administration of deferiprone, a blood-brain-barrier permeable iron

chelator reduced jimpy mouse lethality at P28 and levels of oligodendrocyte apoptosis in the corpus callosum.

Deferiprone (3-hydroxy-1,2-dimethyl-4(1H)-pyridone) is registered in the United States and Europe for the treatment of iron overload in patients > 6 years with thalassaemia major when current chelation therapy is contraindicated or inadequate. Deferiprone in combination with another chelator is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction. Deferiprone has been used in patients (children and adults) with different neurological disorders in treatment studies.

Study objective

This study has been transitioned to CTIS with ID 2024-511968-81-00 check the CTIS register for the current data.

Studying the effect of deferiprone on the motor function of patients with Pelizaeus-Merzbacher disease.

Study design

This is an open-label, non-randomized explorative study with historical control group to evaluate (1) efficacy on motor function in patients with PMD, (2) potential major beneficial effects of deferiprone on quantitative MRI parameters relevant to brain white matter integrity and VEP/AEP and (3) the relationship between deferiprone and possibly efficacy-related biomarkers in an exploratory analysis.

Patients with genetically proven PMD and a brain MRI compatible with the diagnosis will be eligible for participation in the study if they have connatal or classic PMD and are between age 6 months and 7 years at screening. For a more detailed comparison, historical controls will be matched as much as possible to the study population based on age at disease onset, duration of disease at study entry, and disease severity category on the basis of the patient*s genotype.

The study will consist of a screening period of 1 to 3 days, followed by an open-label, non-randomized treatment period of 1 year. After this period, deferiprone will be prescribed off-label to those patients wishing to continue the study until all patients have completed at least 1 year of deferiprone.
A target of 5(-10) patients are planned to receive deferiprone treatment at a dose of 25 mg/kg/day. Deferiprone will be administered as an oral solution in 2 daily doses (in the morning and in the evening) and in addition to the usual standard of care.

The total study duration will depend on the time needed to recruit the planned number of patients. This is expected to be 1 year.

The study will be conducted in a multicentre setting (locations VUmc and AMC of Amsterdam UMC) in Amsterdam, The Netherlands).

Intervention

oral administration of deferiprone oral solution 25 mg/kg/d in 2 single doses

Study burden and risks

Based on (1) the effect of deferiprone on PMD oligodendrocytes in vitro and (2) results of previous studies using deferiprone in a mutant mouse model that is representative of human PMD, deferiprone may ameliorate PMD in patients. As all classic and connatal PMD patients have an infantile disease onset, the present study cannot be conducted without participation of patients belonging to this group. The strongest beneficial effects of deferiprone on the neurological phenotype are expected to occur in children with severe disease, early in the disease course, when neurons and axons are still relatively intact. In addition to the twice daily intake of deferiprone, the burden of study participation includes:
• Regular (every 3 months) control visits to the site (VU University Medical Center; VUmc) for physical and neurological examinations, motor function assessment, temperature, blood pressure and heart rate measurements, and blood sampling (full blood count, iron parameters, zinc).
• Assessment of motor function by physiotherapist at day -10 to 0, 180 and 365 including video documentation.
• EEG registration at day -10 to 0, 180 and 365.
• Brain MRI scans (at day 0 and day 365). The MRI procedures will take place under superficial anaesthesia aiming at spontaneous respiration. At VUmc, annual / biannual MRI scans under superficial anaesthesia are routine practice for patients with a leukodystrophy, including PMD.
• Weekly capillary blood sampling for full blood count. Capillary blood sampling is also necessary when children have fever > 38 degree C.
• CSF and blood sampling for biomarker analysis when the child is under anaesthesia for MRI.
• Skin biopsy (2mm diameter) for fibroblast cultures when the child is under anaesthesia for his first MRI (if fibroblasts are not yet available).
• Bi-annual assessments (by standard questionnaires and scales) of quality of life and disability.

In summary, given the severity of the disease with (1) poor quality of life and severe disability of PMD patients, (2) the absence of effective treatment options, (3) non-clinical evidence indicating that deferiprone may ameliorate PMD, (4) its proven safety in children including infants, and adults with

hematological conditions, and (5) the absence of risks related to determination of the study parameters versus standard procedures, the potential value of this study for future PMD patients outweighs the risks and burden for participating PMD patients.

Main risk of deferiprone is leukopenia. This can lead to serious infections. Weekly monitoring of full blood count is an established method to prevent severe neutropenia and its complications. This monitoring will be performed using capillary blood sampling (as for glucose testing in patients with diabetes), close to home or at home, minimising burden of this intervention for the patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Genetically proven PMD with a clinically relevant mutation in PLP1 (missense mutation or duplication/triplication) and an MRI compatible with the diagnosis.
- Present age between 6 months and 8 years of age.
- Connatal or classic form of the disease (defined as not being able to sit without support and/or a mutation predicting this form, e.g. PLP1 duplication or higher copy numbers; known missense mutations associated with severe forms).

Exclusion criteria

- important comorbidity as another genetic disease
- liver or kidney disease
- neutropenia in patient's history
- severe iron deficiency

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	04-04-2021
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ferriprox

Generic name:	deferiprone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-06-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-511968-81-00
EudraCT	EUCTR2021-000070-29-NL
CCMO	NL74668.029.21