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

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Deferiprone rescues oligodendrocytes in children with PMD and leads to improved myelination and motor function.

Ethische beoordeling	Niet van toepassing
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27427

Bron
NTR

Verkorte titel
Treat PMD

Aandoening

Pelizaeus-Merzbacher disease (PMD)

Ondersteuning

Primaire sponsor: VUmc
Overige ondersteuning: ZonMW

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Gross motor function: Gross Motor Function Measure (GMFM) and Gross Motor Function Classification System for Metachromatic Leukodystrophy (GMFCS-MLD)

Toelichting onderzoek

Achtergrond van het onderzoek

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 affected boys, first symptoms are usually congenital nystagmus and muscular hypotonia, evolving to spasticity over the years. 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. Brain MRI shows severe myelin deficit.

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. All genetic defects lead to failure of oligodendrocyte lineage maturation, defective myelination and subsequently axonal damage. In an in vitro PMD model, mutant OPCs demonstrated severe lipid oxidative stress, abnormal iron metabolism and sensitivity to extracellular iron, normalizing with iron chelation using deferiprone. The positive effect of iron chelation was also demonstrated in a mouse model for PMD, the jimpy mouse. Given those effects of deferiprone, already registered for treatment of iron overload, we propose to test this drug in a small group of children with PMD for significant effects on motor function (primary outcome) and brain myelination (main secondary outcome).

Doel van het onderzoek

Deferiprone rescues oligodendrocytes in children with PMD and leads to improved myelination and motor function.

Onderzoeksopzet

0, 3, 6, 9 and 12 months

Onderzoeksproduct en/of interventie

Treatment with deferiprone (25 mg/kg/d in 2 doses)

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Males with 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 7 years of age.
- Connatal or classic form of the disease (defined as not being able to sit without support at age 18 months or, in younger children, a mutation predicting this form, e.g. PLP1 duplication or higher copy numbers; known missense mutations associated with severe forms).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Clinically asymptomatic.
- Comorbidity with another genetic defect.
- Presence of an unrelated serious condition (eg, developmental anomaly, cardiac, liver, blood or kidney disease or malignancy).
- Participation in another clinical study with therapeutic intervention.
- Unable or unwilling to come to the VUmc site as required by the protocol.
- Unable to undergo MRI due to metal-containing implants, such as cochlea implant, neurostimulator or pacemaker.
- Family situation in which adherence to the study medication or follow-up procedures cannot be guaranteed.

- Known allergy or hypersensitivity to deferiprone or to any of the other components of the formulation used in this study.
- Iron deficiency (serum ferritin must be above 500 µg/l). If ferritin is lower, treatment with low-dose iron may be initiated and participation reconsidered after 3 months if ferritin is normalised.
- History of neutropenia in the last 12 months (absolute neutrophile count < 1.5 X 109/l)

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-04-2021
Aantal proefpersonen:	7
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9195
Ander register	METC VUmc : follows

Resultaten