Low dose iron chelation as TReatment of Oxidative damage in Sickle cell disease

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Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20240

Bron
NTR

Verkorte titel
TROS study

Aandoening

Sickle cell disease

Ondersteuning

Primaire sponsor: Amsterdam UMC location AMC.
Overige ondersteuning: AMC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

- To assess efficacy of treatment with deferasirox on sickling as evaluated by change in Point of Sicking (PoS, expressed in mmHg), as quantified by the Oxygenscan. Maximum efficacy is defined as the lowest PoS measured during the treatment period relative (%) to the mean PoS at baseline (before treatment).
- To evaluate safety of deferasirox (signs of iron or other electrolyte deficiency), relationship of deferasirox to AE and SAE; number of medication discontinuations.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:
Sickle cell disease (SCD) is a devastating inherited hemoglobinopathy, characterized by hemolysis, vaso-occlusive crises and organ damage resulting in reduced life expectancy. Oxidative stress is a major pathophysiological factor in SCD playing a significant role in the SCD-related microvascular dysfunction, vaso-occlusion, inflammation and organ damage. Chronic life-long intravascular hemolysis with the resulting excessive levels of cell-free heme and iron is the major cause of increased production of reactive oxygen species (ROS) in SCD. The cell-free heme rapidly releases its iron which is the main driving force of redox reactions. The hydrophobic heme also rapidly intercalates into the plasma membrane of (endothelial) cells where it releases its iron. This potentiates cell damage by catalyzing non-enzymatic generation of ROS. Endothelial cells are a major target of oxidative stress in SCD, mainly due to its proximity to cell-free heme and iron.
By inactivating NO, cell-free ferrous hemoglobin reduces nitric oxide (NO) bioavailability, limiting the important vasodilative, anti-thrombotic and anti-inflammatory properties of NO. Since the ongoing and unremitting release of iron is the major cause of oxidative stress in SCD, it is imminent to investigate the role of iron chelators as antioxidative therapy in this disease.
Iron chelators have been shown to protect various cells, including red blood cells (RBCs) and endothelial cells, against oxidative toxicity. We recently found that sequestration of free iron by the iron-chelator deferoxamine blocked activation of neutrophils and their release of neutrophil extracellular traps (NETs) by sera of SCD patients (preliminary data). NETs have been demonstrated to be toxic, especially, to endothelial cells.
In this study we will test the hypothesis that treating sickle cell patients with low doses of readily available iron chelators might reduce oxidative stress by capturing the excessively released intravascular cell-free iron. We will determine whether treatment with iron chelators results in decreased sickling of RBCs, oxidative stress, neutrophil activation, inflammation, endothelial activation and hypercoagulability and ultimately reduced disease severity. If the hypothesis is confirmed in this pilot dose-finding study, a larger randomized controlled clinical trial will be initiated.

Objective:
To study the safety and efficacy of deferasirox as treatment of oxidative stress in adult subjects with sickle cell disease.

Doel van het onderzoek

Sickle cell disease (SCD) is a devastating inherited hemoglobinopathy, characterized by hemolysis, vaso-occlusive crises and organ damage resulting in reduced life expectancy. Oxidative stress is a major pathophysiological factor in SCD playing a significant role in the SCD-related microvascular dysfunction, vaso-occlusion, inflammation and organ damage. Chronic life-long intravascular hemolysis with the resulting excessive levels of cell-free heme and iron is the major cause of increased production of reactive oxygen species (ROS) in SCD. The cell-free heme rapidly releases its iron which is the main driving force of redox reactions. The hydrophobic heme also rapidly intercalates into the plasma membrane of (endothelial) cells where it releases its iron. This potentiates cell damage by catalyzing non-enzymatic generation of ROS. Endothelial cells are a major target of oxidative stress in SCD, mainly due to its proximity to cell-free heme and iron.
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Onderzoeksopzet

0, 2 weeks, 4 weeks, 6 weeks, 12 weeks

Onderzoeksproduct en/of interventie

Once daily deferasirox, starting with the lowest dose of 360 mg per day during 6 weeks

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. High performance liquid chromatography confirmed diagnosis of HbSS or HbSβ0 genotype.
2. Aged 18-65 years
3. Written informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Blood transfusion in the preceding four months
2. Already using iron chelation due to iron overload
3. Ferritin levels of <50 µg/L and/or transferrin saturation of < 0.20.
4. LDH of < 300 U/L
5. Pregnancy or the desire to get pregnant in the following 6 months
6. Impaired renal function of GFR < 60 ml/min/1,73m2 (CKD-EPI).
7. Known allergic reaction to deferasirox.
8. Other somatic or cognitive condition disturbing adherence to study treatment

Onderzoeksopzet

Opzet

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

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	10-03-2021
Aantal proefpersonen:	10
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Ja

Ethische beoordeling

Positief advies

Datum:	03-09-2020
Soort:	Eerste indiening

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	NL9265
Ander register	METC AMC : 2021_007

Resultaten