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

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20240

Source
NTR

Brief title
TROS study

Health condition

Sickle cell disease

Sponsors and support

Primary sponsor: Amsterdam UMC location AMC.
Source(s) of monetary or material Support: AMC

Intervention

Outcome measures

Primary outcome

- 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.

Secondary outcome

- To evaluate RBC degradation as expressed by phosphatidylserine (PS) exposure on the outer surface of RBC membrane and markers of hemolysis (cell-free heme, lactate dehydrogenase (LDH), bilirubin, reticulocytes and hemoglobin
- To evaluate the effect of deferasirox on RBC HbS percentage
- Effect of deferasirox on levels of non-transferrin bound iron (NTBI) and labile plasma iron (LPI).
- To evaluate the effect of deferasirox on oxidative stress as expressed by intracellular metabolomics and by plasma levels of AGEs
- To evaluate the effect of deferasirox on in vitro adhesion of RBCs
- To evaluate the effect of deferasirox on endothelial activation as reflected by plasma levels of soluble vascular adhesion molecule-1 (sVCAM-1) and von Willebrand factor antigen (VWF:Ag)
- To evaluate the effect of deferasirox on neutrophil activation as measured with flow cytometry and in vitro NET formation

Study description

Background summary

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.

Study objective

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Study design

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

Intervention

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

Contacts

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Eligibility criteria

Inclusion criteria

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

Exclusion criteria

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

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	10-03-2021
Enrollment:	10
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Ethics review

Positive opinion

Date:	03-09-2020
Application type:	First submission

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
NTR-new	NL9265
Other	METC AMC : 2021_007

Study results