The role of Red cell characteristics, Angiogenesis, Viscosity and Oxygenation in the pathophysiology of Sickle cell related retinopathy (RAVOS study)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haemoglobinopathies
Study type	Observational invasive

Summary

ID

NL-OMON53639

Source
ToetsingOnline

Brief title
RAVOS study

Condition

- Haemoglobinopathies
- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
sickle cell disease related retinal damage, sickle cell retinopathy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: beursaanvragen; inmiddels beurs toegekend door Stichting UitZicht

Intervention

Keyword: Angiogenesis, Pathophysiology, Sickle cell retinopathy

Outcome measures

Primary outcome

1. The difference in red blood cell characteristics (point of sickling) between patients with and without (P)SCR in both genotypes

2. The difference in plasma levels of parameters representing the level of systemic angiogenesis activity (CD105, VEGF, CTGF and angiopoietin-2) between patients with and without P()SCR in both genotypes

3. The difference in oxygenation of the retina by assessing the vessel density with angio-OCT and by assessing the oxygen saturation in the retinal arterioles and venules with the oxymap scan in patients with and without (P)SCR in both genotypes

4. The difference in whole blood viscosity between patients with and without (P)SCR in both genotypes

Secondary outcome

1. Association between retinal vessel density assessed by OCT-angiography, oxygen saturation assessed by an Oxymap scan and red blood cell characteristics (deformity, adhesion and point of sickling upon hypoxia)

2. Association between sex, age, and genotype and the biomarkers of angiogenesis

3. Association between hemoglobin, and HbF and biomarkers of angiogenesis

4. Associations between whole blood viscosity and genotype

Study description

Background summary

Sickle cell disease (SCD) is characterized by chronic hemolysis and recurrent microvascular occlusion, resulting in chronic inflammation, increased endothelial adhesiveness, local ischemia and organ damage. This process can affect almost every organ, which can lead to significant morbidity and mortality. Interestingly, a large clinical variability is noticed between individuals with SCD which is currently not well understood. SCD is predominantly seen in individuals of African, Middle Eastern, Mediterranean or Asian descent, but is most prevalent in sub-Saharan countries. Worldwide, more than 300.000 individuals are born with SCD every year. While the prevalence is significantly lower in Western Europe, the numbers are rising due to the increase of migration, making SCD an increasingly important health problem in Western Europe.

In this project, we focus on sickle cell related retinal damage. The retina is very sensitive to ischemic damage, resulting in sickle cell retinopathy (SCR). SCR can be divided in non-proliferative retinopathy (NPSCR) and proliferative retinopathy (PSCR). The latter is characterized by the development of neovascularization progressing to scarring, which can lead to vitreous hemorrhage or retinal detachment. These complications can drastically impair the visual acuity. Therefore, regular ophthalmologic screening is recommended by performing a dilated eye examination every one or two years, starting from the age of ten years. However, the frequency of individual screenings is not well defined, since evidence is lacking. However, there is a remarkable difference in the prevalence of, in particular PSCR, between patients with the HbSS and HbSC genotype. Patients with the combined heterozygosity (HbSC) do more frequently have PSCR despite the fact that the clinical presentation and frequency of other sickle cell-related complications in HbSC patients is milder as compared to patients with homozygous SCD (HbSS).

SCR results from a combination of ischemic vascular disease and secondary angiogenesis, but it is unknown which factors play a significant role in the pathogenesis. Studies on this subject are still in an early phase. The aim of this study is to get more insight in the pathogenesis of (P)SCR.

Study objective

The aim of this study is to get more insight in the pathogenesis of (P)SCR by comparing: (1) Red cell characteristics (deformability and point of sickling in

hypoxia measured by the Oxygenscan), (2) Angiogenesis by determining several biomarkers of angiogenetic activity in plasma samples, (3) Whole blood viscosity and (4) Oxygenation by the assessment of vessel density in the retina by the angio-OCT and by the assessment of the oxygen saturation in the retinal vessels with the Oxymap scan between patients with and without (P)SCR in both genotypes.

Study design

The Oxygenscan is a new method to determine ex vivo the deformability of red blood cells as a function of the partial pressure of oxygen. OCT angiography is a non-invasive routinely used device at the department of Ophthalmology to assess vessel density and macular thinning as markers of impaired oxygenation. The Oxymap scan is a non-invasive device, which will be used to assess the oxygen saturation in retinal arterioles and venules.

In our specialized teaching hospital, more than 300 adult patients with SCD have been systematically screened on all forms of organ damage including retinopathy. For this study, 80 adult patients with SCD with the HbSS or HbSC genotype will be selected for inclusion. For both genotype groups, 20 patients without SCR and 20 patients with PSCR will be included. When these numbers cannot be achieved, patients with non-proliferative SCR will be included to achieve 40 patients per genotype. Patients will receive a complete ophthalmologic examination (best corrected visual acuity, slit lamp examination, dilated fundus examination and OCT angiography) to determine their current status of retinopathy. Blood samples will be drawn for the analysis of the red blood cell characteristics including adhesiveness, deformability and point of sickling by Oxygenscan (as described above). Information on other SCD characteristics (e.g. patient demographics and sickle cell related organ damage) will be retrieved from the operational clinical database. To determine the role of angiogenesis, plasma levels of VEGF (vascular endothelial growth factor), CTGF (connective tissue growth factor), CD105 (endoglin) and angiopoietin-2 will be assessed in these blood samples using ELISA (enzyme linked immunosorbent assay) kits. To determine the role of whole blood viscosity, we will use a cone/plate viscometer (Brookfield DVII+ with CPE40 spindle, Brookfield Engineering Labs, Natick, MA, USA).

Study burden and risks

Included patients will not experience direct advantages of their participation. However, their participation will increase knowledge on risk factors of (P)SCR and might therefore improve health care for SCD patients. We aim to collect the blood samples during planned venepuncture for routine care (thus: no extra risks for the patient). Furthermore, we request patients to fast 8 hours prior to the venepuncture (or, if fasting is not feasible, to consume a low-fat breakfast). As we also plan the venepunctures in the morning to avoid

unnecessary long fasting, we deem the risk for the patients low.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Minimum age of 18 years
• HbSC or HbSS genotype
• Recent ophthalmologic examination (up to 2 years prior) or (willingness to attend) upcoming examination

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Age below 18 years
• Genotype other than HbSC or HbSS
• No recent ophthalmologic examination and no intention to visit the outpatient clinic for ophthalmic and hematologic examination
• Participation in trials with either crizanlizumab, voxelotor or mitapivat.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-06-2023
Enrollment:	80
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	22-07-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	07-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	24-05-2024
Application type:	Amendment
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
CCMO	NL81111.018.22