NeutrOphil acTivity and dIversity (phenotype) in Sickle Cell disEase and their changes after treatment; The NOTICE study

Published: 20-01-2020
Last updated: 10-04-2024

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

Summary

ID

NL-OMON52543

Source
ToetsingOnline

Brief title
NOTICE

Condition

- Haemoglobinopathies

Synonym
Hereditary blooddisorder, Sicklecell anaemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: AMC foundation;Sanquin Landsteiner laboratory

Intervention

Keyword: Fenotypes, Hemoglobinopathy, Neutrophil, Sickle cell disease

Outcome measures

Primary outcome

Primary endpoint of this studie is the difference in activity and phenotypes of neutrophils in patients with sickle cell disease compared to those of healthy controls.

We aim to address the following questions:

- Is neutrophil activity (as measured by flow cytometry and in vitro release of NETs) altered in patients with SCD and does this differ in various circumstances, such as VOC/steady state?

- Which subtypes (anti-inflammatory/pro-angiogenic (N2) vs. pro-inflammatory (N1)) of neutrophils are present in steady state SCD? Is there a relation with hemolytic vs. vaso-occlusive phenotype of SCD?

- How does the neutrophil phenotype alter during vaso-occlusive crisis with increased inflammation and hypoxia as a result of this vaso-occlusion?

Secondary outcome

- The effect of hydroxyurea and red blood cell transfusion on neutrophil phenotype and activity in SCD

- The relation of neutrophil phenotype and activity with iron overload in transfused patients

- Formation of aggregates between neutrophils and platelets

- To elucidate and identify stimulating signals in the vascular microenvironment that drive phenotypic switching of neutrophils. Potential candidates are inflammatory cytokines, danger signals such as cell-free heme and labile iron and pro-angiogenic factors.

- We will identify prime candidates that correlate with disease severity and neutrophil phenotypic changes in in vitro blocking experiments.

- Is sickle red blood cell deformability as measured by Oxygen-scan (LORRCA) associated with neutrophil activation and phenotype?

- To evaluate the relation between the above mentioned markers during painful crisis and clinical parameters of disease severity (pain score, duration of hospitalization, time to next crisis/readmission and other acute complications of painful crisis such as ACS).

Study description

Background summary

Sickle cell disease is a severe hereditary hemoglobinopathy that results in a reduced qualitity of life and life expectancy. Uptill now, only one FDA approved drug is available specifically for sickle cell disease, which has side effects and does not provide enough results for the majority of patients. New therapeutic options are desired. From previous research, we know that neutrophils play an important role in the development of microvascular obstruction and sickle cell disease-related complications. Even in steady state, neutrophilia is associated with severity of disease. Evidence is emerging of different neutrophil phenotypes, with different characteristics. Their precise role in sickle cell disease and the potential therapeutic value are not well understood. This could possibly be a new therapeutic target.

Study objective

The overall aim of this project is to delineate the role of neutrophil activity and diversity in the pathogenesis of acute (e.g. vaso-occlusive crisis (VOC)

and Acute chest syndrome (ACS)) and chronic complications in sickle cell didease and its potential applicability in a clinical setting. We will aim to address the following questions:
To evaluate neutrophil activity and diversity (pro- or anti-inflammatory phenotype) in sickle cell disease both in steady state and during painful vaso-occlusive crisis and the potential relation with disease severity. Furthermore, effects of treatment with hydroxyurea and red blood cell transfusion on neutrophil activity and phenotype will be evaluated .

Study design

We will measure neutrophil activity and phenotype cross-sectionally, in a cohort of patients with SCD that are in steady state (n=30). Within this steady state population, we will evaluate neutrophil activity and phenotype in patients starting with hydroxyurea (n=30) longitudinally both before start (baseline), after 4 weeks and at 3 months after using the optimal hydroxyurea dose. Another group of steady state patients using or starting with chronic transfusion therapy (n=10) will be included for measurements just before the transfusion and 24-48 hours after the transfusion. In addition, we will measure neutrophil activity and phenotype in patients admitted to the hospital because of vaso-occlusive crisis (n=20). Part of these VOC patients we will try to include in the Flevohospital. We estimate this will be a 6 vs 14 spread (since the AMC is a bigger hospital with more SCD patients). However this numbers will also depend on the current pandemic, since now relatively more SCD patients are transferred to the Flevohospital, but this can differ. SCD patients receiving allogeneic stem cell transplantation will be included for measurements before and 3-6 months after complete engraftment (n=5). Race-matched non-SCD volunteers will be included as healthy controls (n=20). Participants will be asked to donate 30 ml of blood at each time point.

Study burden and risks

Blood draws will be combined as much as possible with sample collection for diagnostic purposes. Risks associated with participation in this study is limited to hematoma at the site of puncture. For children venipuncture will always be combined with blood draws for diagnostic purposes. There is no individual benefit to participation in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1.Sickle cell disease patients (age >= 6 years) with high performance liquid chromatography (HPLC) confirmed diagnosis of HbSS, HbSβ0-thalassemia, HbSC or HbSβ+- thalassemia genotype
2. Willing and able to provide written informed consent
3. For the steady state/transfusion/hydroxyurea subgroup: visiting outpatient clinic
4. For the subgroup of patients during painful crisis: inclusion should be performed within 36 hours of admission to the hospital

Exclusion criteria

1. Unable to sign informed consent
2. VOC within 4 weeks of the outpatient clinic visit (steady state subgroup)
3. Pregnancy
4. Active cancer

5. Chronic HIV infection
6. Use of immunosuppressive drugs

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-02-2020
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	20-01-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2022
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	NL71277.018.19