The Effect of Crizanlizumab on Cerebral Perfusion and Oxygenation in Sickle Cell Patients (CSEG101ANL01T)

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To study the effect of crizanlizumab on the hemodynamics of the cerebral vasculature (CBF and CVR)

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON54849

Source
ToetsingOnline

Brief title
SMART study

Condition

- Red blood cell disorders
- Blood and lymphatic system disorders congenital

Synonym
Sickle cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Industrie,Novartis

Intervention

Keyword: cerebral perfusion, crizanlizumab, sicklecell disease, vaso-occlusive crises

Outcome measures

Primary outcome

To assess the effect of crizanlizumab on the cerebral vascular reserve capacity

(CVR)

Secondary outcome

Secondary outcome:

1. To assess the effect of crizanlizumab on cerebral blood flow (CBF).

2. To determine the effect of crizanlizumab on neurocognitive function

(processing speed).

3. To determine the effect of crizanlizumab on the Quality of Life.

Exploratory outcomes:

1. To determine the effect of crizanlizumab on cerebral oxygen utilization and

oxygen extraction fraction (CMRO2 and OEF).

2. To determine the effect of crizanlizumab on cardiovascular biomarkers

(NTproBNP and TRV).

3. To determine the effect of crizanlizumab on biomarkers of oxidative stress

and endothelial damage (AGE*s, VWFag and VCAM-1).

4. To determine the effect of crizanlizumab on neutrophil activity,

pro-inflammatory properties and oxidative burst capacity.

5. To determine the effect of crizanlizumab on neutrophil-platelet adhesion as

measure of neutrophil adhesiveness.

Study description

Background summary

In sickle cell disease (SCD), acute anemia increases the risk for silent cerebral infarcts (SCI), despite having elevated cerebral blood flow (CBF) to compensate anemia. In previous research, we showed that patients with SCD have an increased resting CBF due to chronic vasodilatation, to compensate for the reduced oxygen availability caused by anemia, vaso-occlusion and chronic inflammation. As a result of this already dilated intracerebral vasculature, there is a diminished capacity to further enhance CBF during episodes of decreased oxygen delivery due to hypoxia, pneumonia or reduced blood pressure, resulting in cerebral ischemia.

By the use of Diamox we are able to temporary increase the cerebral blood flow, as a result of maximal vasodilatation of the cerebral vasculature. The rate of increase in cerebral blood flow is called vascular reserve capacity. In a previous trial with a cohort of adult sickle cell patients, we demonstrated that the vascular reserve capacity is strongly reduced in patients with sickle cell disease confirming their vulnerable state with respect to cerebral ischemia.

Crizanlizumab is a new drug that is has been studied in a large international placebo-controlled trial, that has demonstrated to prevent vaso-occlusion in several preclinical models by preventing cellular adhesion to the activated endothelial surface. Recurrent vaso-occlusion of the microvasculature is responsible for tissue ischemia and reperfusion injury, resulting in organ damage.

Organs that have demonstrated to be typically vulnerable to recurrent ischemia are the brain, kidneys, spleen and the bones. Since crizanlizumab is specifically targeting the enhanced cellular adhesion in the microvasculature, thereby preventing vaso-occlusion, tissue ischemia and reperfusion injury, we hypothesize that crizanlizumab may improve cerebral perfusion.

Given the slow progression rate of silent strokes in patients with SCD only a large placebo-controlled trial with a long follow up would be needed to elucidate whether crizanlizumab can prevent silent infarcts. Therefore robust surrogate markers of cerebrovascular perfusion/oxygenation are needed to be able to evaluate the ameliorating effect of crizanlizumab on cerebral perfusion in a small group of patients in a limited time period.

Study objective

To study the effect of crizanlizumab on the hemodynamics of the cerebral vasculature (CBF and CVR)

Study design

Single center, open label intervention study with crizanlizumab. In this study, 20 adult patients with SCD (HbSS or HbSβ0-thalassemia) will be treated with crizanlizumab for 12 months. The study procedures consist of echo, MRI and laboratory assessments that will be performed at baseline, 3 months 6, months (no MRI and no echo) and 12 months upon crizanlizumab administration. Neurocognitive performance will be assessed at baseline and 12 months following crizanlizumab administration.

Intervention

Crizanlizumab infusion over 30 minutes, every 4 weeks for a period of 12 months

Study burden and risks

Potential risk of adverse events due to treatment with crizanlizumab. MRI is harmless, Diamox infusion has proven to be save in patients with SCD and venipuncture is routine in patients with SCD. Parameters obtained by blood drawn in this study will be used clinically as well. Presumably, participation is associated with minimal burden and risks. As cranial MRI is not routinely performed in adults with SCD, coincidental findings are potentially beneficial. The studied population represents the group of patients with the highest disease severity, and is, thus, representable.

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

1. Documented SCD genotype (HbSS, HbSβ0-thalassemia) which may be based on history of laboratory testing or must be confirmed by laboratory testing during screening.
2. Age 18 and above
3. For participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at
least 90 days prior to participation and with no anticipated need for dose adjustments
4. Participants, who if female and of child bearing potential, are using highly effective
methods of contraception from study start to 30 days after the last dose of study drug, and who if male are willing to use barrier methods of contraception, from study start to 30
days after the last dose of study drug.
5. Participant has provided documented informed consent or assent (the informed consent
form [ICF] must be reviewed and signed by each participant; the participant*s legal representative or legal guardian, and the participant*s assent must be obtained).

Exclusion criteria

1. No informed consent has been given
2. Contra-indication for MRI or acetazolamide
3. Female who is breast feeding or pregnant.
4. Patients who are receiving regularly scheduled blood (RBC) transfusion therapy (also

termed chronic, prophylactic, or preventive transfusion) or have received a RBC transfusion for any reason within 90 days before participation.
5. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days prior participation.
6. History of overt stroke (defined as a symptomatic stroke confirmed by CT or MRI).
7. Hypertension or uncontrolled diabetes mellitus
8. Hepatic dysfunction characterized by alanine aminotransferase (ALT) >4 × ULN.
9. Participants with clinically significant bacterial, fungal, parasitic or viral infection which
require therapy:
• Participants with acute bacterial infection requiring antibiotic use should delay
screening/enrollment until the course of antibiotic therapy has been completed.
• Participants with known active hepatitis A, B, or C
10. Severe renal dysfunction (estimated glomerular filtration rate <30mL/min).
11. History of malignancy within the past 2 years prior to participation requiring chemotherapy and/or radiation (with the exception of local therapy for non-melanoma
skin malignancy).
12. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior
to consent including but not limited to the following:
• Unstable angina pectoris or myocardial infarction or elective coronary intervention.
• Congestive heart failure requiring hospitalization.
• Uncontrolled clinically significant arrhythmias.
13. Any condition affecting drug absorption, such as major surgery involving the stomach or
small intestine (prior cholecystectomy is acceptable).
14. Participated in another clinical trial of an investigational agent (or medical device) within
30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently
participating in another trial of an investigational agent (or medical device)
15. Medical, psychological, or behavioral conditions, which, in the opinion of the
Investigator, may preclude safe participation, confound study interpretation, interfere
with compliance, or preclude informed consent.
16. Receipt of erythropoietin or other hematopoietic growth factors within 28 days of signing
ICF or anticipated need for such agents during the study.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-01-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	crizanlizumab
Generic name:	crizanlizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2021
Application type:	First submission
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
EudraCT	EUCTR2020-003601-66-NL
CCMO	NL74869.018.20