The effect of GBT440 on cerebral perfusion and oxygenation (GBT440-MRI side study)

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1. To assess the effect of increased hematocrit on cerebral perfusion as depicted by CBF and CVR.2. To determine the effect of GBT440 on oxygen saturation of the cerebral vasculature and the oxygen local consumption.3. Determine the dose response...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Haemolyses and related conditions
Study type	Observational invasive

Summary

ID

NL-OMON46527

Source
ToetsingOnline

Brief title
GBT440-MRI side study

Condition

- Haemolyses and related conditions

Synonym
Sickle cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Global Blood Therapeutics

Intervention

Keyword: cerebral perfusion, GBT440, Magnetic Resonance angiography, oxygenetion

Outcome measures

Primary outcome

In our current research we have shown that low hemoglobin levels raise resting CBF and leave patients with inadequate CVR. Our hypothesis is that GBT440 will result in higher hemoglobin levels, reduced hemolysis and decreased sickling resulting in lower viscosity, reduced CBF and increased CVR. The effect on oxygen utilization is uncertain given the contrasting effects on circulating oxygen content versus high oxygen affinity, but will be investigated in parallel.

Secondary outcome

nvt

Study description

Background summary

Our laboratory has demonstrated that CBF is increased to maintain oxygen delivery in patients with anemia2,3. However, this compensatory cerebral vasodilation may not be without costs. Blood vessels have limited capacity to dilate4. The proportion that CBF can be increased under metabolic stress, relative to the baseline flow, is known as the cerebrovascular reserve (CVR). CVR is typically 40%-70% in healthy control subjects, but is much lower in subjects with anemia because of their already increased resting brain blood flow4. A decreased CVR does not directly cause damage, but it leaves the brain vulnerable to ischemic insults because the brain*s oxygen reserve capacities (a combination of increased flow and extraction) can no longer compensate for decreased oxygen delivery or increased metabolic demand. This two-hit hypothesis is supported by studies linking acute anemic events to strokes in sickle cell patients5. Nighttime desaturations, which are relatively minor but repetitive, cause strokes over years6,7.

GBT440 is a new compound that stabilizes hemoglobin in its oxy-form thereby correcting the oxygen affinity to normal values. In a phase 1 and 2 studies it has been demonstrated that GBT440 is safe and is able to reduce the hemolytic rate in patients with SCD resulting in a significant rise in hemoglobin concentration. In addition, GBT440 has demonstrated to reduce the number of circulating sickled red cells and plasma levels of specific markers of vascular distress such as ICAM and sP-selectin.

Study objective

1. To assess the effect of increased hematocrit on cerebral perfusion as depicted by CBF and CVR.
2. To determine the effect of GBT440 on oxygen saturation of the cerebral vasculature and the oxygen local consumption.
3. Determine the dose response relation of GBT440 on the above parameters.
4. To determine the effect on shear stress of GBT440.

Study design

In current studies, we have built up ample experience with all mentioned MRI techniques and we consider ourselves as one of the few labs in the world that can perform these technically demanding measurements non-invasively using MRI. Patients will be analyzed by MRI after inclusion in the HOPE trial before the start of the study medication and 3 months after initiation of study medication. Since patients will be randomized between high dose GBT440, low dose GBT440 and placebo, three groups will be analyzed with respect to the effect of GBT440 on cerebral perfusion.
The following measurements of the cerebral perfusion will be performed by MRI:
1. CBF will be measured by PCASL in SCD.
2. CVR will be assess by the administration of acetazolamide which is a carbonic anhydrase inhibitor that produces a powerful cerebral vasodilatory effect comparable to 5% inhaled CO2.8,9
3. Cerebral oxygen utilization is measured by MRI technique by T2 relaxation under spin tagging (TRUST).

Study burden and risks

MRI is harmless, the ACZ injection has been declared safe and venapunction is routine in patients wtih 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 therefore

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. Subjects have to be included in the HOPE study (GBT440-031 - NL60453.018.17)

Exclusion criteria

1. Subjects who are excluded from the HOPE study (GBT440-031 - NL60453.018.17)
2. No informed consent has been given
3. Contra-indication for MRI or acetazolamide

4. Previous symptomatic stroke

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO

Date:	03-05-2018
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
CCMO	NL65103.018.18