Combined Molecular Microscopy for Therapy and Personalized Medication in Rare Anaemias Treatments

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(i) identification and cellular characteristics of red blood cells from patients with altered ion homeostasis and delivery of novel and easy-to-use diagnostics for rare anemia*s, for patients with: a) a known primary defect in the ion channels of...

Ethical review	Not approved
Status	Will not start
Health condition type	Red blood cell disorders
Study type	Observational invasive

Summary

ID

NL-OMON41732

Source
ToetsingOnline

Brief title
CoMMiTMenT

Condition

- Red blood cell disorders

Synonym
anaemia, herideritarty hemolytic anaemia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Europesie Unie

Intervention

Keyword: ion conductance scanning microscopy optofluidic microscopy, rare anaemias, red blood cells

Outcome measures

Primary outcome

o Red blood cell hematology parameters; cytology and biochemistry

o Red blood cell morphology

o Quantity and size distribution of (RBC) microvesicles

o Eosin-5-maleimide (EMA) binding on surface of red blood cells

o Intracellular Ca2+, Na+ and K+ levels

o Na+ uptake and K leak by red blood cells

o Activity of transporters NHE, NKCC, Na/K-ATPase, Gardos channes and other

channels/conductance

o Conductance and patch-clamp measurements of red blood cells

o CD47 presentation

o 2,3-DPG measurement

o Band 3 clustering

o ATP concentration

o Glutathione measurement: ratio between GSH/GSSG

o Osmotic fragility

o Density

o Enzyme activity

o Osmotic gradient ektacytometry (LoRRca MaxSis)

o Deformability (LoRRca MaxSis)

o PS exposure

o DNA analysis for candidate ion channels by PCR and Next Generation

Sequencing: Band3, spectrin, ankyrin, protein 4.2, EPB72/STOM, KCNN4, TRPC6,

GRIN1, GRIN2A, GRIN2C, GRIN2D, GRIN3A, GRIN3B, SLC9A1, ATP11C, XK, AQP1, AQP3,

ATP1A2, ACHE, CAII, SLC16A1, VDAC3, TSPO, SLC25A4, CLCN2, PIEZO1

Secondary outcome

Not applicable

Study description

Background summary

Anaemia, which is defined as a haemoglobin concentration less than 6,82 * 8,06 mmol/L depending on gender and age, affects 1.6 billion individuals worldwide. Approximately 10% of these individuals are affected by rare anaemia (RA). This disease group includes approximately 90 different types of red blood cell (RBC) diseases, of which 80% are hereditary or congenital in nature. As the pathophysiology of the majority of these RA is poorly understood, the appropriate treatment is often ineffective or even lacking. Although the total number of affected individuals is substantial, the diversity in the underlying causes has resulted in limited interest from the pharmaceutical industry.

Recent studies indicate that several RA are associated with altered cellular ion homeostasis. These deficiencies may directly cause the disease, as in hereditary xerocytosis, overhydrated hereditary stomatocytosis, familial pseudohyperkalaemia, cryohydrocytosis and certain types of spherocytosis. There are scenarios in which RA may be due to structural RBC abnormalities due to congenital membrane protein defects, e.g., hereditary spherocytosis, haemoglobinopathies (e.g., sickle cell anaemia, thalassemia and glucose transporter GLUT1 mutations, which cause paroxysmal exertion-induced dyskinesias, inducing haemolytic anaemia by a cation leak.

A third category of RA associated with altered cellular ion homeostasis are enzyme deficiencies (e.g., phosphofructokinase deficiency). Moreover, it appears reasonable to assume that novel, unidentified ion homeostasis disturbances may significantly contribute to anaemia pathophysiology and may constitute an important group of undiagnosed cases of RA. The CoMMiTMent Consortium has various objectives for the specific types of hereditary

haemolytic anaemia. (A) For the well-known and well-described types of hereditary haemolytic anemia, such as sickle cell anaemia, treatment concepts will be developed. (B) For other, more rare types of HHA, the pathophysiology and pathways leading to ion channel disturbances will be investigated. (C) Last but not least, for the yet undiscovered types of HHA, new diagnostic tools will be developed. The UMC Utrecht will mainly focus on objectives B and C.

Together with the consortium partners in the CoMMiTMenT project we will implement existing tools and/or laboratory tests, such as intracellular calcium, sodium and potassium measurements as well as tools to measure ion channel activities. We also will investigate the role of nanoparticles or microvesicles, which are bud off from the plasma membrane of the red cell during cellular stress, and might act as biomarkers for these specific diseases. One of the triggers for the release of microvesicles from the red cell membrane is an elevation of intracellular calcium and therefore these microvesicles might act as biomarkers of ion channel disturbances of the red cell. Microvesicles might also be involved in the comorbidities which patients with hereditary haemolytic anaemia are suffering from, since microvesicles have prothrombogenic and proimflammatoiry properties
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The CoMMiTMenT consortium includes small and medium sized enterprises. Together with the clinical partners, the consortium will develop a new diagnostic tool. This tool will be called µCOSMOS and will be a combination of two already existing techniques: Optofluidic Microscopy-based Cell Sorting (OMiCS) and Scanning Ion Conductance Microscope (SICM). OMiCS optically measure cells in a microfluidic system. Cells will be sorted with a laser based on their size, shape or abnormal morphology. SICM then scans the surface of the sorted cells with an electric probe. This measurement with SICM will be non-invasive and will result in a topographic image of the red cell at a nanometer resolution. Ultimately, the development of this µCOSMOS device will result in a system which is able to select and study diseased red cells from a very heterogeneous population of cells. Current diagnostic tools only study the total population of red blood cells.

Study objective

(i) identification and cellular characteristics of red blood cells from patients with altered ion homeostasis and delivery of novel and easy-to-use diagnostics for rare anemia*s, for patients with:
a) a known primary defect in the ion channels of the erythrocyte, e.g. stomatocytosis
b) Secondary defect(s) of ion channels of the erythrocyte. For example, unfunctional ion channels due to shortage of energy caused by metabolic disorders (e.g. phosphofructokinase-defiency) or upregulated NMDA-receptors in sickle cell anaemia causing influx of calcium25.
c) Patients with an unknown cause for haemolytic anaemia, of which

yet-unidentified ion channel disturbances may be the primary or secondary cause of hemolysis.

(ii) identification of microvesicles as biomarkers or diagnostic tools and to study their clinical relevance in (rare) haemolytic anaemias

Study design

The proposed study is a mono-center descriptive cohort study.

In this study patients with hereditary xerocytosis, overhydrated hereditary stomatocytosis, familial pseudohyperkalaemia, cryohydrocytosis, certain types of spherocytosis, hyperphosphatidylcholine haemolytic anaemia, sickle cell anaemia, thalassemia syndromes, RBC enzymopathies (i.e., disorders of glycolysis and glutathione metabolism) and patients with an unknown cause of hereditary hemolytic anemia will be recruited from Academic partner hospitals in Europe. The recruitment of patients will also take place in academic hospitals in Europe we have international and academic relation with, inter alia:

* University Medical Centre Utrecht, The Netherlands
* Consorci Institut d*Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain
* Foundation IRCCS Ca* Granda Ospedale Maggiore Policlinico, Oncohematology Unit, Physiopathology of Anemias Unit, Milan, Italy
* Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal

Shipping and transfer of patient material from hospitals across to the University Medical Centre Utrecht, The Netherlands and vice versa will be carried out according to the *Material Transfer Agreement' as shown in the K6. CoMMiTMenT Consortium Agreement and K6. CoMMiTMenT Grant Agreeement* as shown in the appendix. Patients in other national and international academic hospitals will be recruited by their local physician.

Study burden and risks

Burden is limited to the donation of 41 ml blood, once of twice. If possibly, all donations will be obtained during regular visits in the University Medical Centre Utrecht. The current study will not be possible without the cooperation of this specific group of patients. The patient does not benefit directly from this study. However, we expect that this study leads to a better understanding of the underlying pathophysiology of the rare anaemia he or she is suffering from. On the long term this may lead to alternative treatments.

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)
Elderly (65 years and older)

Inclusion criteria

Know and unknown cause of (heriditary) hemolytic anaemia, low Hb, high plasma hemoglobin and/or or family member to be known with (heriditary) hemolytic anaemia

Exclusion criteria

Transfusion received within 90 days

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:	80
Type:	Anticipated

Ethics review

Not approved

Date:	14-04-2015
Application type:	First submission
Review commission:	METC NedMec

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	NL48958.041.14