Mechanisms of immune selection of GPI-deficient hematopoietic stem cells in paroxysmal nocturnal hemoglobinuria (PNH)

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To study the role of GPI-deficiency in susceptibility of hematopoietic stem cells to cytotoxic T lymphocyte (CTL) and Natural Killer (NK) cell mediated lysis in the pathogenesis of PNH.

Ethical review	Approved WMO
Status	Pending
Health condition type	Haemolyses and related conditions
Study type	Observational invasive

Summary

ID

NL-OMON30207

Source
ToetsingOnline

Brief title
PPNH06

Condition

- Haemolyses and related conditions

Synonym
Paroxysmal nocturnal hemoglobinuria

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Pathogenesis, PNH

Outcome measures

Primary outcome

in vitro susceptibility of hematopoietic stem cells of PNH and aplastic anemia patients and a clone of blood cells with deficient expression of GPI-anchored proteins for cytotoxic lysis.

Secondary outcome

The presence of autoreactive T, NK and NKT cell populations in blood of PNH and aplastic anemia patients with a clone of blood cells with deficient expression of GPI-anchored proteins.

Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by an acquired mutation of the X-linked PIG-A gene in hematopoietic stem cells, resulting in a clone of blood cells bearing this mutation. The PIG-A gene is essential for the expression of glycosyl phosphatidyl inositol (GPI) anchored proteins at the cell membrane. GPI anchored proteins include complement inhibitors CD55 and CD59. Deficiency of these molecules on the cell surface of erythrocytes leads to hemolysis upon complement activation, and associated symptoms such as severe anemia, hemoglobinuria, abdominal pain, dysphagia and erectile dysfunction. Next to intravascular hemolysis, patients have a high risk of thrombosis and many patients have associated bone marrow failure. Symptoms only occur when the PNH clone has expanded to a certain level. It is not known why a PNH clone expands.
Interestingly, PNH is closely related to aplastic anemia (AA), which is considered to result from auto-immune mediated bone marrow damage. A significant proportion of AA patients have subclinical PNH clones and overt PNH often develops during the course of AA. Therefore, auto-immune mediated bone marrow failure may be involved in the pathogenesis of PNH as well. In a setting of autoimmune mediated bone marrow failure, it is hypothesized that

hematopoietic stem cells deficient in expression of GPI-anchored proteins survive immunological attack whereas their GPI-positive counterparts do not. This immunological selective advantage of GPI deficient hematopoietic stem cells could explain expansion of a PNH clone.

Study objective

To study the role of GPI-deficiency in susceptibility of hematopoietic stem cells to cytotoxic T lymphocyte (CTL) and Natural Killer (NK) cell mediated lysis in the pathogenesis of PNH.

Study design

We will study differential susceptibility of GPI-positive and GPI-negative cells for lysis by high-affinity cytotoxic T lymphocytes recognizing antigens on HSC in vitro. This will be investigated in cytotoxicity assays using cell lines and hematopoietic stem cells from PNH and AA patients as target cells. To elucidate the role of individual GPI-linked proteins in causing differential susceptibility, we will perform blocking studies of GPI-anchored proteins in cytotoxicity assays, again using cell lines and hematopoietic stem cells from PNH and AA patients as target cells.
We will characterize potentially autoreactive T cell, Natural Killer (NK) cell and Natural Killer T (NKT) cell populations in blood samples drawn from PNH patients using immunophenotyping. Autoreactive T, NK or NKT cell populations will be expanded and assessed functionally for proliferative capacity, cytokine production and most importantly, for cytolytic activity towards GPI positive and GPI negative hematopoietic stem cells.

Study burden and risks

The risks of a sternal bone marrow aspiration include bleeding and infection but occur very rarely. Risks of blood drawing include a hematoma, infection or bleeding at the puncture site.

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

PNH patients
Aplastic anemia patients with a clone of blood cells with deficient expression of GPI-anchored proteins
Age 18 years or older
Informed consent

Exclusion criteria

Not capable of determining will

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2007
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL15625.091.06