Blood Outgrowth Endothelial Cells (BOECs) to study the pathophysiology of von Willebrand disease and the feasibility of in vitro correction of von Willebrand factor defects

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1. To establish optimized approaches for the isolation and characterization of BOECs and iPSC-ECs2. To further explore the biology of VWF, the pathophysiology of different subtypes of VWD and the role of VWF as a signalling protein in for example...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational invasive

Summary

ID

NL-OMON47740

Source
ToetsingOnline

Brief title
VWD characterization and correction in BOECs

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym
Von Willebrand Disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,CSL Behring,Subsidie van LSBR

Intervention

Keyword: siRNA, Von Willebrand Disease, Von Willebrand Factor

Outcome measures

Primary outcome

As this study is a basic science, experimental in vitro, non-therapeutic study,

there are no efficacy parameters.

However the outcome of the study will be: optimized isolation and

characterization procedures of BOECs, iPSC-ECs, and iPSC-MKs; identification of

new pathophysiologic mechanisms of VWD; establishment of the feasibility of

silencing of dominant-negative mutant VWF alleles using RNA-targeted silencing

or CRISPR/Cas9-editing in BOECs and iPSC-ECs.

Secondary outcome

Not applicable

Study description

Background summary

Von Willebrand factor (VWF) plays an essential role in primary hemostasis. It is synthesized in endothelial cells and megakaryocytes and is stored in Weibel-Palade bodies and *-granules, respectively. Qualitative and quantitative defects of VWF lead to the most common, inherited bleeding disorder von Willebrand disease (VWD). Patients with types 1 and 2 VWD are usually heterozygous for missense mutations in the VWF gene that exert a dominant-negative effect of the mutant allele on the wild type allele resulting in additional quantitative and qualitative defects of VWF. Current therapy for

VWD is based on inducing the release of endogenously synthesized VWF or infusion of exogenous VWF concentrates. However, factor concentrates have a short half-life, are very expensive and will not correct the negative effects of the still circulating mutant VWF. A new therapeutic strategy could be to silence the expression of the mutant VWF allele by RNA-targeted therapy or CRISPR/Cas9-editing to decrease the synthesis of the mutant VWF and as a consequence increase the synthesis of normal VWF. For the development of new therapeutic strategies a good understanding of the pathophysiology of VWF mutations is necessary. The most optimal model for studying the VWF biology and RNA-targeted silencing are the blood outgrowth endothelial cells (BOECs). An alternative approach to obtain patient specific VWF producing cells is to reprogram peripheral blood mononuclear cells (PBMCs) into induced pluripotent stem cells (iPSCs) that can subsequently be differentiated into endothelial cells (iPSC-ECs) and megakaryocytes (iPSC-MKs).

Study objective

1. To establish optimized approaches for the isolation and characterization of BOECs and iPSC-ECs
2. To further explore the biology of VWF, the pathophysiology of different subtypes of VWD and the role of VWF as a signalling protein in for example angiogenesis using BOECs and iPSC derived endothelial cells and megakaryocytes/platelets.
3. To develop in vitro a therapeutic strategy for VWD by silencing of dominant-negative mutant VWF alleles using RNA-targeted silencing or CRISPR/Cas9-editing in BOECs and iPSC-ECs

Study design

The study is a multicenter, basic science, experimental in vitro, non-therapeutic study.

Study burden and risks

The burden for the participants is minimal as the research is restricted to a single 30 minutes visit to the hospital including a short interview on medical history and medication use and a venepuncture with a total maximum blood draw of 70 mL.

Participants may be requested to participate in repeated sampling, however this will be maximised to three times and the repeated sampling will be a maximum of 50 mL of blood. For repeated sampling the participants will be asked for a new informed consent.

The risk of venepuncture is negligible. Proper manual compression of the puncture site for a few minutes will prevent any bruises.

Patients do not directly benefit from this research. Their blood samples will be used in a fundamental research project only.

The study is focused on pathophysiologic aspects and potential new therapeutic approaches of VWD and can only be performed in this study population.

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

Patients with von Willebrand disease (any subtype), age 18 years or older.
Family members of patients with von Willebrand disease (may or may not be affected themselves), age 18 years or older.
Healthy control (not known with von Willebrand disease or other hemostatic

disorders), age 18 years or older.

Exclusion criteria

< 18 years of age
Unable to visit the LUMC or Erasmus MC
Unable to give written informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-05-2016
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	17-12-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	22-12-2016
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL54591.058.15

Study results

Date completed:	01-12-2021

Actual enrolment: 80

Summary results
Trial is onging in other countries