Genetic Determinants of the Outcome of Immune Tolerance Induction therapy in patients with severe haemophilia A and inhibitors

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The aim of this study is to identify genetic determinants that are associated with successful immune tolerance induction in patients with haemophilia A and inhibitors.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Blood and lymphatic system disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON54650

Source
ToetsingOnline

Brief title
GO ITI Study

Condition

- Blood and lymphatic system disorders congenital

Synonym
coagulation disorder, Hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Stichting Steun Emma van het Academisch

Medisch Centrum

Intervention

Keyword: Genetic determinants, Hemophilia, Immune tolerance induction, Inhibitors

Outcome measures

Primary outcome

The genetic determinants under study include copy number variations and single nucleotide polymorphisms in FCGR2A, FCGR2B, FCGR2C, FCGR3A, FCGR3B, F8 genotype, F8 haplotype, SNPs in the IL-10, TNF-α and CTLA-4 genes.

The main study outcome is the cumulative incidence of completely successful ITI associated with potential genetic determinants.

Secondary outcome

The secundary study outcome is the cumulative incidence of partially successful ITI associated with potential genetic determinants.

Study description

Background summary

What is known: The bleeding tendency in patients with haemophilia A can be effectively corrected by intravenous administration of the deficient FVIII. Regular prophylactic infusions of FVIII enable people with haemophilia to have a normal life. However, treatment with FVIII may be complicated by the formation of inhibiting antibodies, directed towards FVIII in 25-35% of the patients. These inhibitors preclude treatment with FVIII products by neutralizing FVIII activity. Even though alternative hemostatic treatments that bypass FVIII are available, it is generally more challenging to treat bleeding and prevent arthropathy in individuals with inhibitors. This results in a greater rate of bleeding complications, disability and costs. Antibody eradication is the ultimate goal of inhibitor management. The only clinically proven strategy is immune tolerance induction (ITI) therapy, which consists of frequent administration of high doses of FVIII. Successful ITI eradicates the inhibitor and restores the efficacy of FVIII replacement therapy with

consequent improvement in the patient*s quality of life. However, 10 to 40% of patients who undergo immune tolerance induction do not achieve immune tolerance.
What is not yet known: It is currently unknown whether genetic factors are associated with the chance of successful immune tolerance induction therapy in patients with severe haemophilia A and inhibitor development.
What this study may add: Knowledge on genetic determinants for inhibitor eradication after immune tolerance induction therapy in haemophilia A will enable the identification of patients who are at an increased risk of failing immune tolerance induction therapy. In these individuals, a tailored, more intensive immune tolerance induction regimen including immune suppressive medication may be needed. Patients with a good prognosis may benefit from avoiding a demanding and costly immune tolerance treatment course and be treated with a less intensive regimen that may nevertheless be effective.
Our hypothesis is that genetic factors are associated with the outcome of immune tolerance induction in patients with haemophilia A and inhibitors.

Study objective

The aim of this study is to identify genetic determinants that are associated with successful immune tolerance induction in patients with haemophilia A and inhibitors.

Study design

This study is an observational multicenter cohort study among patients with severe haemophilia A who underwent immune tolerance induction therapy.

Study burden and risks

The participants* burden is a single blood draw for DNA collection during a routine venipuncture at a outpatient clinic visit. The risk associated with drawing extra blood is minimal. No direct benefit is expected from participation in this study. Participation in this study may have benefits for future patients with haemophilia with inhibitors. Because inhibitor development occurs during childhood, it is important that children participate in this study.

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)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

1. Severe haemophilia A, defined as a baseline FVIII activity of <0.01 IU mL-1.
2. A current or a history of inhibitor development.
3. Received or is currently receiving immune tolerance induction therapy of any kind.
4. Written informed consent.

Exclusion criteria

Refused informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-11-2016
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	13-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2020
Application type:	Amendment
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	NL53406.018.15