PROFIT: PRospective studie OF Immune Tolerance induction (ITI)

Published: 13-03-2019
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Primary Objective:Improve the knowledge about the immune response during FVIII/FIX replacement therapy in patients with haemophilia A and B respectively. This involves both the mechanism of: 1) primary tolerance induction to FVIII/FIX in previously…

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

Summary

ID

NL-OMON48806

Source
ToetsingOnline

Brief title
PROFIT

Condition

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

Synonym
bleeding disorder, coagulation disorder

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anti-FVIII/anti-FIX antibody, Haemophilia, Immune tolerance induction, Inhibitor

Outcome measures

Primary outcome

The main study endpoint is the (absence or presence of an) antigen-specific immune response to FVIII or FIX, i.e. detectable anti-FVIII or anti-FIX antibodies (inhibitors) in respectively haemophilia A and B.

This can be subdivided into the following:

1) The development of an antigen-specific immune response to FVIII or FIX (i.e. an inhibitor) during the first treatment episode in PUPs.

* Defined as an inhibitor titer > 0.3 BU.

2) The eradication of an antigen-specific immune response / induction of tolerance to FVIII or FIX during ITI.

* Defined as an inhibitor titer <= 0.3 BU (2 times), recovery >= 66% and T* FVIII >=6 hours / T* FIX >= 12 hours.

In order to evaluate the mechanism of (primary and secondary) tolerance induction, the following parameters will be measured:

1. Using modified Bethesda assay:

- FVIII/FIX inhibitor titer; read-out of the presence or absence of an anti-FVIII / anti-FIX immune response

2. Using flow cytometry:

* Pro-inflammatory/immunogenic parametersdeterminants:

- Number and percentage of FVIII/FIX-specific reactive B-cells

- Number and percentage of FVIII/FIX reactive CD4+ T-cells (Teff)

* Anti-inflammatory/regulatory parametersdeterminants:

- Number and percentage of regulatory B cells (Bregs)

- Number and percentage of regulatory T-cells (Treg)

- Teff/Treg ratio

- Number and percentage of myeloid derived suppressor cells (MDSCs)

3. Using Luminex:

- Cytokine levels (concentration), differentiation between pro-inflammatory (TNF, IL-1, IL-2, IL-6) and anti-inflammatory cytokines (TGF-beta, IL-4, IL-10)

Explanation:

The endpoint, i.e. 1) inhibitor development yes/no and 2) inhibitor eradication yes/no during ITI, will be related to the (change in) immune profile and FVIII- or FIX reactivity in order to evaluate the mechanism of (primary and secondary) tolerance induction.

Hereby the results will be analyzed both intra-individually as interindividually:

I. Intra-individually; to detect changes in the antibody-specific immune response during factor replacement therapy, including ITI

II. Interindivdually / (explorative) subgroup analysis; comparison of the antibody-specific immune response between different groups:

- Patients who develop an inhibitor versus patients who don't develop an inhibitor.
- In ITI: Patients, that are succesfully treated with ITI versus patients, in which ITI failed.

Secondary outcome

The secondary study parameters are aimed at providing a detailed characterization of antigen-specific cells and their function related to FVIII or FIX.

Specifically, we will measure:

1. Using cell culture-based functional assays:

- T-cell activation assay: Activation/regulatory status of CD4+ T-cells after stimulation with FVIII or FIX (expressed as percentage of cells that are positive for the following markers: CD25, CD69, PD1, ICOS, CTLA4)
- Treg suppressor assay: Suppressive function of regulatory T-cells, as measured with a Treg suppressor assay, expressed as percentage of inhibition

2. Using ELISA:

- Amount and (iso)type of FVIII/FIX-specific antibody

(In case of haemophilia A: reactivity to FVIII heavy chain vs. light chain)

Study description

Background summary

Nowadays the development of neutralizing antibodies against factor VIII (FVIII) or factor IX (FIX), so called inhibitors, is one of the most serious complications during the treatment of haemophilia A and haemophilia B respectively. This complication occurs in approximately 33% of all patients with severe haemophilia A and in 5-10% of all patients with haemophilia B, mostly during the first treatment period. As a consequence of these inhibitors traditional replacement therapy with FVIII or FIX becomes ineffective, making it necessary to switch to other, often less effective and more expensive, treatment options. This all leads to a significant increase in morbidity and treatment costs and a decrease in patients' quality of life.
The treatment used to eliminate these inhibitors is called Immune Tolerance Induction (ITI). During this therapy repeated administration of high doses of FVIII or FIX ultimately leads to eradication of the inhibitor in approximately 2/3 of all patients.
However, the pathophysiology of inhibitor development and the working mechanism of ITI is not fully elucidated. This lack of knowledge is mainly the result from the lack of clinical information about the phenotypic and functional changes of the different FVIII- or FIX-specific immune cell populations that are involved in the immune responses during factor replacement therapy in general and during ITI more specifically. Many information is derived from animal models. However, the utility of these models is limited as recapitulating the frequent infusion schedule used in ITI protocols in mice is technically difficult and unethical and moreover translation of data from animal models to clinical practice in humans is very challenging.
Therefore the best way to answer some of the questions regarding the mechanism of tolerance induction, both natural and artificial in case of ITI, is to follow patients during (the first phases of) factor replacement therapy, including ITI, and to set up a biobank.
By prospectively collecting blood samples during factor replacement therapy and evaluating the immunological responses during this therapy, important insight in the mechanism of inhibitor development and tolerance induction can be obtained. This insight might eventually result in better prevention of inhibitor development and/or an improvement of the high demanding treatment of inhibitors by ITI. Moreover information about tolerance induction is not only beneficial for haemophilia, but also applies to many different other diseases, especially auto-immune and auto-inflammatory disorders.

Study objective

Primary Objective:
Improve the knowledge about the immune response during FVIII/FIX replacement therapy in patients with haemophilia A and B respectively. This involves both

the mechanism of:
1) primary tolerance induction to FVIII/FIX in previously untreated patients (PUPs),
as well as
2) secondary tolerance induction during ITI in (treated) patients who developed inhibitors.

Specifically, this immune response means the changes over time in the different FVIII- or FIX-specific immune cell populations, the number and function of regulatory immune cells and cytokine production.

Secondary Objective(s):
To set up a biobank to collect blood samples which provide valuable data for future research on the development of inhibitors and/or immune tolerance induction in patients with haemophilia.

Study design

Single centre, prospective observational cohort study.

Study burden and risks

In order to participate in this study patients will be prospectively followed, whereby the first blood withdrawal will take place during the first phase of the treatment (< 5 EDs).
If patients don't develop an inhibitor, a blood withdrawal for study purposes will be taken tree times more (at 5-10 EDs, 15-20 EDs and 50 EDs).
If patients develop an inhibitor and start with ITI, they will be followed from the start of ITI until 2 years after the finish of ITI. During this period clinical data about the treatment regimen and the course of the inhibitor titer will be collected and regularly bloodsamples will be taken for immunological research.
The blood withdrawals for study purposes will always be combined with an already scheduled outpatient clinic visit and venipuncture, both as part of standard of care.
Therefore no extra visit to the hospital and no extra venipunctures are necessary in order to participate in this study. The only difference is that during some venipunctures a large volume of blood will be taken than normally (8 ml to 27 ml extra, related to the patients' body weight). Based on an average duration of ITI of 1-2 years (in which during the first half year blood samples will be taken every month and thereafter every 3 months) and a 2 year follow-up after termination of ITI (in which blood samples will be taken 2 times a year), in totaal about 10-20x 8-27 ml blood will be withdrawn for study purposes.
Hereby the volume of blood is small enough and the interval between the venipunctures long enough that we don't expect any adverse events or other

risks.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

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)

Inclusion criteria

1. Diagnosis of severe haemophilia A OR haemophilia B. ;AND
2A) Previously Untreated Patient (PUP, < 5 exposure days (EDs))
OR
2B) Treatment with ITI due to presence of inhibitor, whereby ITI is defined as the administration of factor VIII or factor IX concentrate according to the local protocol with the aim of inducing tolerance ;AND

3. Willing and be able to understand the study information and sign the informed consent form. In case of minor patients, this will be done by a proxy.

Exclusion criteria

- Documented auto-immune disease

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-03-2019
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	13-03-2019
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	18-04-2019
Application type:	Amendment
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	NL63007.041.18