Immune tolerance induction (ITI) in patients with hemophilia A: pathophysiologic mechanisms and difference in efficacy between various types of factor VIII (FVIII) products

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Two main research questions:- improving the knowledge of the pathofysiologic mechanisms of immune tolerance induction (ITI)- determining what type of factor VIII product (based on pathophysiology and an in-vitro model of ITI) is the most effective...

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

Summary

ID

NL-OMON49249

Source
ToetsingOnline

Brief title
HIP study: Haemophilia A Immune tolerance induction Project

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: Bayer,Interne gelden

Intervention

Keyword: hemophilia A, immune tolerance induction, inhibitors, ITI

Outcome measures

Primary outcome

- Immunologic analysis with a comparison between patients with and without inhibitor:

* Amount and phenotype of FVIII specific B-cells, ie B-naïve, B-memory, B plasma cell.

* Amount of regulatory B-cells

* Amount of myeloid derived suppressor cells (MDSCs)

* Amount and phenotype of FVIII specific CD4-cells (T-cells), ie T effector vs. T regulator.

* Activation and proliferation status of CD4+ T-cells

* Function of regulatory T-cells

* Amount and type of FVIII antibodies

* Cytokine production (pro- versus anti-inflammatory)

With the abovementioned analyses we will test what will cause tolerance, i.e. on one side the elimination or absence of FVIII-specific effector B- and T-cells or on the other hand the induction of regulatory cells (regulatory B- and T-cells and MDSCs). Moreover some functional assays will be performed to

evaluate not only differences in quantity, but also possible differences in the function / quality of effector and regulatory T-cells,

Finally the role of pro- vs. anti-inflammatory cytokines will be evaluated (which is also indirectly related tot the ratio between pro-inflammatory and regulatory cells).

Secondary outcome

- Creating an in-vitro human model of ITI and testing different factor VIII products with regard to their potency to generate an inflammatory or more tolerogenic respons

* Co-culture of CD4+ T-cells (naive or FVIII-specific) with B-LCL (EBV immortalized B-cells, acting as antigen presenting cells) and addition of different types of FVIII producs

* After 24 hours measurement of T-cell response:

1) Amount and subtype of CD4+ T-cells (effector vs. regulatory T-cells)

2) T-cel activation and proliferation status

3) Cytokine profile (pro- vs. anti-inflammatory)

Study description

Background summary

The most serious complication in the treatment of hemophilia A is the development of so called *inhibitors*, inhibitory antibodies against factor VIII, which occurs in almost 30% of all patients with severe Hemophilia A1. As a consequence of this inhibitor formation traditional replacement therapy becomes ineffective, making it necessary to switch to alternative hemostatic therapies by using bypassing agents, which are less efficient, more costly and moreover require a lot of intravenous injections because of a very short half-life. This all causes a high morbidity and negatively influences patients*

quality of life.
The therapy to eliminate inhibitors is the so called 'Immune tolerance induction' (ITI), a therapy which is characterized by frequent administration of factor VIII with the objective of inducing tolerance. This treatment is succesful in approximately 2/3 of all patients. However the workingmechanism is largely unknown and moreover many different protocols are used, for example with different doses of factor VIII en different factor VIII products.
Since hemophilia A is still a relatively seldom disease it*s not easy to perform large randomized controlled trials. Instead many information is derived from case reports, case series and retrospective cohorts. In-vitro studies can provide important additional information, especially with regard to pathophysiologic mechanisms.
This study is aimed at gaining a better understanding in the pathophysiologic mechanisms of ITI and determining what would be the optimal fVIII concentrate to use. Since the high burden of inhibitors in hemophilia A and also the high costs and intensity of ITI this is essential information for further improving the treatment of hemophilia A.

Study objective

Two main research questions:
- improving the knowledge of the pathofysiologic mechanisms of immune tolerance induction (ITI)
- determining what type of factor VIII product (based on pathophysiology and an in-vitro model of ITI) is the most effective during ITI

The objective of the study is optimization of ITI, so that this treatment becomes more successful, less stressful for patients and possibly also less costly.

Study design

Cross-sectional single-center observational study.

Study burden and risks

The extent of the burden and risks associated with participation are different between adults and children.
Adults:
Participation of the study will mean one venipuncture, with the withdrawal of 54 ml blood. If possible, this venipuncture will be combined with a regular outpatient visit and with a regular venipuncture.
Risks of the venipuncture are formation of a small, local hematoma and pain/discomfort. If the puncture is combined with a regular venipuncture the additional burden will only be the withdrawal of a larger amount of blood than normally. Since it is still a small amount of blood the risks of anemia or

dizziness/hypotension will be considered negligible.

Children:
For children participation of the study will always be combined with a regular outpatient clinic visit en scheduled venipuncture. The extra burden due to participation of the study will therefore only consist of the withdrawal of more blood (22 ml) than normally, without any extra invasive procedures. Since the very small amount of blood that will be taken extra, we consider the risks of this (for example anemia or hemodynamic consequences) negligible.

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)

Inclusion criteria

- Age: 6 years and older
- Previously confirmed Hemophilia A
- Previously and frequently (> 50 ED) treated with factor VIII
- Willing and be able to understand the study information and sign the informed consent form;Different subgroups:
* 10 adults with an inhibitor (5 patients with mild or moderate hemophilia A, 5 patients with severe hemophilia A)
* 10 adults without an inhibitor after successful ITI
* 20 patients (10 adults, 10 children age > 6 years) without an inhibitor and without a history of ITI

Exclusion criteria

- Documented history of persisting severe anaemia (defined as haemoglobin <6.0 mmol/L for men and women)
- Other haematologic or immunologic comorbidity
- Recent (< 3 months) or actual use of immunosuppressive drugs (< 9 months for rituximab, < 3 months for other immunosuppressive drugs)
- Active infection at the moment of blood withdrawal

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):	09-11-2017
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO Date:	13-10-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-01-2019
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	NL60611.041.17