I-SWITCH: Changes in Immune profiles after SWITCH to a different factor VIII product

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1. Evaluation of the change in immunologic profile after switch to a different FVIII product, ie analysis of (FVIII specific) B- and T-cell subtypes, amount and function of regulatory T cells (Tregs) and cytokine production. 2. Determining the risk...

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

Summary

ID

NL-OMON46126

Source
ToetsingOnline

Brief title
I-SWITCH

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: Interne gelden.

Intervention

Keyword: antibody, factor VIII, hemophilia A, inhibitor

Outcome measures

Primary outcome

Change in immunologic profile after switch to a different FVIII product, ie analysis of (FVIII specific) B- and T-cell subtypes, amount and function of regulatory T cells (Tregs) and cytokine production.

Secondary outcome

Incidence of inhibitor formation during first year after switch to a different factor VIII product.

Comparison between the four different switches:

- Switch of pd-FVIII to rFVIII

- Switch of rFVIII to other type of rFVII

- Switch of pd-FVIII to rFVIII-Fc

- Switch of rFVIII to rFVIII-Fc

Study description

Background summary

Hemophilia A is a serious bleeding disorder characterized by a deficiency of factor VIII (FVIII). Treatment traditionally consists of administration of the deficient coagulation protein. The past decennia a lot of progress has been made in the development and improvement of many different types of FVIII concentrates.
Nowadays the most serious complication in the treatment of hemophilia A is the development of so called *inhibitors*, neutralizing antibodies against factor VIII, which occurs in almost 30% of all patients with severe hemophilia A. As a consequence of these inhibitors 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 life3.

Since the important negative impact of inhibitors a lot of attention is paid to the prevention of inhibitor formation as well as the elimination of inhibitors, once they are formed. Considering prevention of inhibitor formation many different risk factors are described, both patient-related and treatment-related. An ongoing and still unresolved issue in the risk of inhibitors is the role of the different FVIII products, whereby there is some evidence that recombinant FVIII is associated with a higher risk of inhibitor formation compared to plasma derived Von Willebrand Factor containing products (pd-VWF/FVIII) FVIII (pd-FVIII).

Another interesting issue is the recent introduction of FVIII products with an extended half-life, for example rFVIII-Fc, which is a fusion protein of rFVIII and the Fc domain of IgG1. The approximately 1.5-fold longer half-life of rFVIII-Fc is caused by the possibility of the Fc-domain to bind to the neonatal Fc receptor (FcRn), which is expressed in many cell types and protects IgG1 and Fc-fusion proteins from lysosomal degradation. The main advantage of this new rFVIII-Fc product is that it requires less intravenous injections, making the treatment of hemophilia less invasive and burdensome. Moreover there are some previous reports that fusion of FVIII (or other haptens) to the Fc-region of IgG has immunomodulatory properties and may induce tolerance. Therefore rFVIII-Fc could have a protective role in the prevention and treatment of inhibitors. Recently this has been confirmed in a hemophilia A mouse study.

Due to national regulations the prescription of coagulation products will change this year and for hemophilia A the number of FVIII products will be limited to the use of three preferred medications, of which two short-acting rFVIII products and the abovementioned rFIII-Fc. Therefore many patients with hemophilia A will have to switch to a different FVIII product.
For some people, both patients and doctors, there is still some reluctance to change FVIII products because of the fear of inhibitor formation. However this is mainly based on some older reports and is not confirmed in more recent studies.

Since hemophilia A is still a relatively rare disease it*s not easy to perform large randomized controlled trials. Instead information to a large extent is still derived from case reports, case series and retrospective cohorts. Due to the abovementioned change in prescription regulations a large cohort of patients will have to switch to a different FVIII product. This switch offers an unique opportunity to prospectively follow these patients and to perform an immunologic analysis, which can provide essential information regarding possible changes in the immunologic profile after switch to a different FVIII product and if there is a difference between the various types of FVIII product

(ie pd-VWF/FVIII vs. rFVIII vs. rFVIII-Fc).
Moreover also the incidence of inhibitor formation will be determined. This all is very valuable information regarding the treatment of hemophilia A.

Study objective

1. Evaluation of the change in immunologic profile after switch to a different FVIII product, ie analysis of (FVIII specific) B- and T-cell subtypes, amount and function of regulatory T cells (Tregs) and cytokine production.

2. Determining the risk of inhibitor formation after switch to a different FVIII product and evaluating if there is a difference in type of FVIII used
4 different comparisons:
- Switch of pd-FVIII to rFVIII
- Switch of rFVIII to other type of rFVII
- Switch of pd-FVIII to rFVIII-Fc
- Switch of rFVIII to rFVIII-Fc

We hypothesize that switch to a different FVIII product is not associated with an increased risk of inhibitor formation. With this prospective cohort study we expect to confirm this hypothesis in order to reduce the fear of changing FVIII products. Moreover the comparison between the different FVIII products and the immunologic analyzes will provide valuable informating regarding the ongoing debate about possible differences in the type of FVIII and the risk of inhibitor formation.

Study design

Prospective cohort study.

Study burden and risks

For participation in the study patients will be subjected to the withdrawal of blood at 3 time points (before switch, 4-6 months after switch and 1 year after switch). At all time points the bloodwithdrawal will be combined with a regular outpatient clinic visit and scheduled venipuncture as part of standard of care. So the additional burden due to participation of the study will be the withdrawal of a larger volume of blood than usual. For patients aged 6-12 years this will be 3 time 11 ml extra, for patients aged 12 years and older this will be 3 times 22.5 ml extra. These quantities are so small that no adverse events are expected.

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 diagnosis of moderate or severe hemophilia A
- Switch to a different FVIII concentrate in 2017
Possible switches:
1: plasma derived FVIII (pd-FVIII) product to recombinant FVIII (rFVIII) product
2: rFVIII to a different rFVIII product
3: pd-FVIII to rFVIII-Fc (fusion protein with a prolonged half-life, consisting of rFVIII and Fc-protien)
4: rFVIII to rFVIII-Fc;- 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 history of persisting severe anemia (defined as hemoglobin <6.0 mmol/L for men and women)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-09-2017
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	06-09-2017
Application type:	First submission
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	NL61452.041.17