The effect of recombinant Factor IX-FIAV in In-vitro thrombin generation in hemophilia A patient samples

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To obtain blood samples from twenty-one adult hemophilia A patients with and without inhibiting FVIII antibodies for biochemical analyses in order to show the efficacy and determine the potency of recombinant FIX-FIAV treatment using thrombin...

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

Summary

ID

NL-OMON47946

Source
ToetsingOnline

Brief title
FIVITAS

Condition

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

Synonym
Hemophilia A; coagulation disorder

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: UniQure NV

Intervention

Keyword: Hemophilia A, In vitro, Recombinant FIX, Thrombin generation

Outcome measures

Primary outcome

Thrombin generation parameters (lag time (main parameter), thrombin peak, time to peak, endogenous thrombin potential) following the addition of purified recombinant FIX-FIAV in vitro.

Secondary outcome

- The correction in clotting capacity (activated Partial Thromboplastin Time, aPTT) following addition of the purified recombinant FIX variant FIX-FIAV to plasma from hemophilia A patients in vitro.
- To assess the effect on thrombin generation when combining FIX-FIAV with approved products used to treat hemophilia A (activated prothrombin complex concentrate (FEIBA), activated factor VII (NovoSeven), a bispecific FVIII-mimicking antibody (emicizumab/HemLibra)) will be determined in the plasma from hemophilia A patients in vitro in order to assess potential induction of a prothrombotic state.
- Baseline FVIII (chromogenic and one-stage), FIX (chromogenic and one-stage), prothrombin, antithrombin, FX, von Willebrand factor (vWF), FVIII inhibitory antibodies, and clotting capacity.

Study description

Background summary

Hemophilia A (HA) is a rare X-linked recessive hereditary bleeding disorder, caused by factor VIII deficiency. Many severe (FVIII level <0.01 IU/ml) hemophilia A patients undergo prophylactic treatment by three weekly infusions of FVIII concentrate to prevent bleeding, especially in joints. Gene therapy with FVIII is presently being developed which normalizes coagulation, reduce bleeding complications and the need for prophylaxis, as shown in recent trials. However, a gradual decrease of FVIII levels after gene therapy has been noted. Taken together, these data support the notion that FVIII-mediated gene therapy might be less than optimal, suggesting that novel approaches are needed. Recently, FIX variants were described which comprise mutations in the FIX protein and can catalyze interactions with FX in the absence of FVIII. One of these FIX variants, FIX-FIAV, has four amino acid difference compared to wildtype FIX. Gene therapy approaches are being developed using an AAV vector to deliver a transgene that encodes for FIX-FIAV, AMT-180, representing a novel avenue to treat hemophilia A patients. Such an approach has proven successful in pre-clinical studies. Normal and hemophilia A mice show an increase in circulating FIX-FIAV levels after gene therapy, and data support improved clotting activity in the absence of FVIII. Safety assessments in these animals demonstrated no elevation of coagulation activation markers, no signs of thrombus formation and no other adverse events. Further, in silico and in vitro assessments showed low immunogenicity risk. In vitro data also support efficacy of this approach, but translational data are limited due to a shortage of HA patient samples. If successful, novel FIX-FIAV gene therapy could be applied in hemophilia A patients with and without inhibitory FVIII antibodies.

Study objective

To obtain blood samples from twenty-one adult hemophilia A patients with and without inhibiting FVIII antibodies for biochemical analyses in order to show the efficacy and determine the potency of recombinant FIX-FIAV treatment using thrombin generation and clotting activity tests in vitro. The blood samples will be taken at trough levels of the respective treatment regime, for example before the next planned dose of FVIII in case of prophylactic treatment.

Study design

Non-randomized, non-interventional, cross-sectional study

Study burden and risks

Only one venepuncture will be performed. Severe hemophilia A patients on prophylactic treatment will be included but just before subsequent treatment with FVIII.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age 18 years or older hemophilia A patients
- Male sex
- Mentally capable of informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Prophylactic treatment with FVIII, with less than 48 hours washout period

between dosages of FVIII
- Patients receiving bypassing therapy such as prothrombin complex (FEIBA), eptacog alfa (NovoSeven) or emicuzimab (HemLibra)
- Any other known hemostatic disorder, inherited or acquired (such as acquired von Willebrand disease etc*)
- Any known liver disease, leading to acute or chronic liver disfunction and/or failure

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-12-2019
Enrollment:	21
Type:	Actual

Ethics review

Approved WMO

Date:	04-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 25584
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL71211.078.19