The effect of recombinant factor IX-FIAV in in vitro thrombin generation in hemophilia A
patient samples; FIVITAS

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON25584

Source
Nationaal Trial Register

Brief title
FIVITAS

Health condition

Hemophilia A;
Gene Therapy;
Thrombin Generation

Sponsors and support

Primary sponsor: Erasmus University Medical Center Rotterdam
Source(s) of monetary or material Support: UniQure N.V.

Intervention

Outcome measures

Primary outcome

- To quantify thrombin generation following addition of the purified recombinant FIX variant FIX-FIAV to plasma from hemophilia A patients in vitro.

Secondary outcome

- To quantify 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 in order to assess potential induction of a prothrombotic state.

- 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.

- Determine the following baseline clotting parameters in the patient plasma samples: FVIII, FIX, prothrombin, antithrombin, FX, von Willebrand factor (vWF), FVIII inhibitory antibodies, and clotting capacity.

Study description

Background summary

Rationale: 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.

Objective: To obtain blood samples from 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 population: Twenty-one adult (>18 years) hemophilia A patients, of whom 7 severe (<0.01 IU/mL), 7 moderate (0.01 to 0.05 IU/mL) and 7 mild (0.05 IU/mL to 0.40 IU/mL); at least 4 of whom have clinically relevant factor FVIII inhibiting antibodies (>0.5 Bethesda units).

Main study parameters/endpoints: FVIII levels, FVIII inhibitor levels, FIX levels, clotting assays and thrombin generation in the absence and presence of purified recombinant FIXFIAV protein comparable to at least 5% FVIII activity; additional assays will also be performed to compare the addition of recombinant FIX-FIAV with approved products used to treat hemophilia A.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: only one venepuncture will be performed. Severe hemophilia A patients on prophylactic treatment will be included just before subsequent treatment with FVIII.

Study objective

Use of FIX-FIAV in vitro is safe and effective in generating an adequate thrombin generation response

Study design

Not applicable

Contacts

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Eligibility criteria

Inclusion criteria

- Age 18 years or older hemophilia A patients
- Male sex
- Mentally capable of informed consent

Exclusion criteria

- 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 emicizimab (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 non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2019
Enrollment:	21

Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	27-06-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47946
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8731
CCMO	NL71211.078.19
OMON	NL-OMON47946

Study results