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

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

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON25584

Bron
Nationaal Trial Register

Verkorte titel
FIVITAS

Aandoening

Hemophilia A;
Gene Therapy;
Thrombin Generation

Ondersteuning

Primaire sponsor: Erasmus University Medical Center Rotterdam
Overige ondersteuning: UniQure N.V.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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Onderzoeksopzet

Not applicable

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	04-12-2019
Aantal proefpersonen:	21
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	27-06-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 47946
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten