Clinical validation of Factor VIII allo-antibody assays in patients with severe hemophilia A (PSTOL 15).

Gepubliceerd: 21-06-2011 Laatst bijgewerkt: 15-05-2024

Clinically validation of the different detection assays for inhibitory factor VIII antibodies.

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

Samenvatting

ID

NL-OMON23098

Bron
Nationaal Trial Register

Verkorte titel
IMPALA

Aandoening

severe haemophilia A patients, low titer assay, factor VIII antibodies, negative Bethesda assay, pharmacokinetic

Ondersteuning

Primaire sponsor: Radboud University Nijmegen Medical Centre
Overige ondersteuning: Radboud University Nijmegen Medical Centre
Pfizer by means of an unrestricted educational grant.
Baxter by means of an unrestricted educational grant.

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. To study the correlation between the antibody levels measured with the different assays and the pharmaco kinetic parameters;
2. To calculate the sensitivity, specificity, negative and positive predictive value of the different assays with respect to the pharmaco kinetics of factor VIII.

Toelichting onderzoek

Achtergrond van het onderzoek

The development of inhibitory allo-antibodies (inhibitors) against factor VIII is a severe complication of haemophilia A (HA)therapy with plasma-derived or recombinant Factor VIII. The incidence of inhibitors in HA patients varies from 2.4 to 52.0 % (average approximately 25 %) and is mainly dependent on the genotype. The development of inhibitors occurs predominantly at the onset of therapy, approximately after 10 to 20 days of exposure to factor VIII products. Therefore it affects mostly children. Given the difficulties associated with the treatment of inhibitors, prediction and prevention of inhibitors following exposure to factor VIII in the patient has become a management priority. Detection of factor VIII allo-antibodies with reliable laboratory assays plays a central role as an early start of immune suppression therapy after inhibitor formation, yields a significantly better outcome.

In this project the primary objective is to address the relevance of several subclasses (inhibiting and non-inhibiting) of antibodies in factor VIII survival in patients with haemophilia A. The subclasses of antibodies can be measured using different antibody detection assays. These assays however, have not yet been validated with respect to factor VIII survival in patients with haemophilia A. In this project we will perform pharmacokinetic studies of factor VIII in patients with severe haemophilia A with and without inhibitors. Specificity, sensitivity, negative and positive predictive value of the available assays will be defined on factor VIII antibody levels and the pharmacokinetic parameters of infused factor VIII. The secondary objective is to determine the importance of factor VIII binding and clearance molecules (non-inhibiting inhibitors, von Willebrand factor, á2-macroglobulin) on factor VIII pharmacokinetics in patients with factor VIII deficiency with or without inhibitors.

We expect that clinical validation of the different factor VIII antibody assays will give more insight into the pathophysiological relevance of factor VIII antibody formation in patients with haemophilia A.

Doel van het onderzoek

Clinically validation of the different detection assays for inhibitory factor VIII antibodies.

Onderzoeksopzet

Blood will be drawn to analyze the initial haemoglobin level and platelet count. If the patient fits the criteria, a baseline blood sample (t=0) will be taken, followed by an injection of the factor VIII concentrate. Blood samples will be taken at different time points to perform PK analysis of facotr VIII. Inhibitor levels will be measured in blood samples of t=0 min.

Onderzoeksproduct en/of interventie

At inclusion by the haematologist blood will be taken for the assessment of hemoglobin concentration, haematocrit value and blood group. During the experimental part of the study, the patients will undergo a pharmacokinetic procedure after receiving a fixed dose plasma-derived or recombinant FVIII.

Patients who have been enrolled will experience overnight fasting the day before the study.At the day of the study, before the start a clinician will examine the patient physically and check the exclusion criteria again. Blood will be drawn to analyze the initial haemoglobin level and platelet count. If the patient fits the criteria, a baseline blood sample (t=0) will be taken, followed by an injection of the factor VIII concentrate. Blood samples will be taken at different time points to analyze the different parameters.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Inclusion criteria for patients with severe haemophilia A without inhibitors are:

1. Less than 1% factor VIII activity (severe clinical phenotype of haemophilia A);

2. No factor VIII infusion for minimally 72 hours;

3. Normal response to factor VIII during bleeding episodes;

4. Normal recovery (>1,5%/U/kg);

5. No recent change in bleeding pattern;

6. No history of an inhibitor.

Inclusion criteria for patients with severe haemophilia A with or at high risk of having factor VIII inhibitors:

1. Less than 1% factor VIII activity (severe clinical phenotype of haemophilia A);

2. No factor VIII infusion for minimally 72 hours;

3. Diminished response to factor VIII compared to past performance:

A. Or: Low recovery of factor VIII;

B. Or: More frequent bleedings and/or a different bleeding pattern;

C. Or: Higher need for FVIII substitution than before.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Exclusion criteria for patients with severe haemophilia A without inhibitors are:

1. Known allergy to plasma proteins;

2. Fever (higher than 38 °C);

3. Clinical indication of liver cirrhosis (echographic indication, enlarged spleen, enlarged liver, decreased platelet count);

4. Hepatitis C treated with interferon within 6 months prior to inclusion;

5. HIV positive;

6. Medication:

A. NSAIDs (non-steroid anti-inflammatory drugs);

B. Specific platelet inhibitors (aspirin, clopidogrel, RheoPro);

C. Antimicrobial medication;

D. Thyroid inhibitors;

E. Selective serotonin re-uptake inhibitors.

7. Hb levels less than 8.0 mmol/l;

8. Platelet counts less than 50*109/ltr;

9. Difficile venous acces;

10. Change of factor VIII concentrate used during the last year.

Exclusion criteria for patients with severe haemophilia A with inhibitors or suspected of having factor VIII inhibitors:

1. Known allergy to plasma proteins;

2. Fever (higher than 38 °C);

3. Clinical indication of liver cirrhosis (echographic indication, enlarged spleen, enlarged liver, decreased platelet count);

4. Hepatitis C treated with interferon within 6 months prior to inclusion;

5. HIV positive;

6. Medication:

A. NSAIDs (non-steroid anti-inflammatory drugs);

B. Specific platelet inhibitors (aspirin, clopidogrel, RheoPro);

C. Antimicrobial medication;

D. Thyroid inhibitors;

E. Selective serotonin re-uptake inhibitors.

7. Hb levels less than 8.0 mmol/l;

8. Platelet counts less than 50*109/ltr;

9. Difficile venous acces.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	04-12-2008
Aantal proefpersonen:	150
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	21-06-2011

Soort: Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 31749
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2808
NTR-old	NTR2949
CCMO	NL19146.091.08
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON31749

Resultaten

Samenvatting resultaten
N/A