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

No registrations found.

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

Summary

ID

NL-OMON23098

Source
Nationaal Trial Register

Brief title
IMPALA

Health condition

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

Sponsors and support

Primary sponsor: Radboud University Nijmegen Medical Centre
Source(s) of monetary or material Support: Radboud University Nijmegen Medical Centre
Pfizer by means of an unrestricted educational grant.
Baxter by means of an unrestricted educational grant.

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

1. Correlation of FVIII pharmaco kinetic parameters and inhibitor levels with von Willebrand factor. The von Willebrand factor may influence pharmacokinetic parameters of factor VIII as von Willebrand Factor (including ABO serology) is the chaperone molecule of factor VIII (Ref 13,14). Therefore it may also affect antibody levels;

2. Correlation of FVIII pharmaco kinetic parameters and inhibitor levels with total and transformed á2-macroglobulin. Factor VIII and á2-macroglobulin share one receptor for clearing the proteins from circulation, the lipoprotein receptor-related protein (LRP). Therefore, á2-macroglobulin levels may influence the pharmacokinetic parameters of factor VIII, factor VIII antibodies as well as the correlation between both in humans as it does affect factor VIII kinetics in mice (ref 15,16,17).

Study description

Background summary

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.

Study objective

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

Study design

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.

Intervention

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.

Contacts

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Eligibility criteria

Inclusion criteria

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.

Exclusion criteria

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.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2008
Enrollment:	150

Type:	Anticipated

Ethics review

Positive opinion
Date: 21-06-2011
Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 31749
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

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

Study results

Summary results
N/A