Detecting Subclinical Joint Bleeding and Inflammation in Haemophilia

Published: 25-07-2019
Last updated: 09-04-2024

Objective part I: To detect subclinical (inflammatory) joint changes using ultrasound and MRI in severe haemophilia patients with low bleeding rates and to correlate these findings with biochemical markers of joint tissue turnover.Objective part II...

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

Summary

ID

NL-OMON55572

Source
ToetsingOnline

Brief title
BEGIN-study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
haemophilia, hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Novo Nordisk,NovoNordisk;Pfizer,Pfizer

Intervention

Keyword: blood, haemophillia, inflammation, joint

Outcome measures

Primary outcome

Part I:

At joint level: Radiological signs of subclinical inflammation defined as synovial hypertrophy on ultrasound (or MRI in case of inconclusive ultrasound findings).

At patient level: Biomarkers for inflammation and biomarkers for cartilage and bone turnover in blood and urine. The biomarkers comprising origin of different joint tissues will be selected and adopted based on the literature on osteoarthritis, which is a rapidly changing area of research.

Part II:

Radiological signs of subclinical bleeding defined as: synovial hypertrophy, MRI detected iron / haemosiderin deposits in joints without a history of bleeding at joint level.

Secondary outcome

At joint level:

- The diagnostic value of physical examination (swelling, warmth) in comparison with synovial hypertrophy detected with ultrasound.
- Occurrence of MRI detectable blood products in joints with joint effusion on ultrasound in the absence of a clinical bleed.

Study description

Background summary

Repeated provoked or spontaneous bleeding into the joints are the hallmark of haemophilia. Recurrent or prolonged joint bleeds eventually lead to synovial hypertrophy, progressive cartilage degradation and bone damage through mechanical and inflammatory joint destruction. Treatment for severe haemophilia is targeted at preventing joint bleeding using intravenous replacement therapy with FVIII/IX (prophylaxis). In clinical practice, prophylaxis is constantly adjusted, based on reported (joint) bleeding, joint assessment and measured FVIII/IX (trough) levels.
There is some evidence, primarily based on X-ray and Magnetic Resonance Imaging (MRI) studies, suggesting that patients with severe haemophilia may suffer from subclinical bleeding. At the Van Creveldkliniek, patients who stopped prophylaxis showed significant progression of arthropathy (joint scores and X-ray) only after 10 years, despite very low reported bleeding rates.
Subclinical bleeding is expected to induce subclinical joint changes such as synovial hypertrophy and inflammation, eventually resulting in osteochondral changes and (progression of) arthropathy. Early detection of subclinical/synovial and/or inflammatory joint changes will allow timely adaptation/intensification of treatment to prevent irreversible damage.

Study objective

Objective part I:
To detect subclinical (inflammatory) joint changes using ultrasound and MRI in severe haemophilia patients with low bleeding rates and to correlate these findings with biochemical markers of joint tissue turnover.

Objective part II:
To evaluate whether there is any evidence of subclinical bleeding on MRI in joints without a history of bleeding.

Study design

Cross-sectional study in a cohort of haemophilia patients aged >=16 years with available longitudinal follow-up (patient records) at the Van Creveldkliniek, UMC Utrecht.

Study burden and risks

Participating patients will spent more time in the hospital at the day of their planned clinical follow-up due to the additional MRI examination. In addition to possible clinically indicated blood test, additional blood samples (29ml)

will be drawn for biomarker evaluation and urine (30ml) will be collected. Patients will not have a direct benefit from participating in this study: their bleeding pattern and current outcome will not change. On long term, patients may benefit from the optimization of treatment due to detailed assessment of outcome and possibilities of treatment with anti-inflammatory drugs.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patient provides written, informed consent;
- Born
o Between January 1, 1970 and January 1, 1988 (METC 11-442)

o After January 1, 1988 and age >=16 years
- Severe haemophilia A (FVIII< 0.01 IU/ml)
- Treated at the Van Creveldkliniek, UMC Utrecht

Exclusion criteria

- History of inhibitor development (>= 5 Bethesda Units* (BU) at any time or 1-5 BU for >=1 year)
- Patients with a history of a major joint bleed in the three months prior to assessment
- Patients with a history of a minor joint bleed in the month prior to assessment
- MRI exclusion criteria, including MRI contraindications as per usual clinical care, such as claustrophobia and metal or electronic implants not compatible with MRI.

*One Bethesda unit (BU) is defined as that amount of inhibitor that results in 50% re-sidual FVIII:C activity in tested plasma mixed with an equal volume of a normal plasma pool (NPP) after incubation for 2 hours at 37°C.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-12-2019
Enrollment:	82
Type:	Actual

Ethics review

Approved WMO Date:	25-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL68186.041.19

Study results

Date completed:	08-02-2022
Results posted:	30-11-2022
Actual enrolment:	79

Summary results
Trial is onging in other countries

First publication
30-11-2022