DDAVP treatment combined with FVIII clotting factor concentrates in patients with mild hemophilia A.

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Primary objectives:To assess the proportion of non-severe hemophilia A patients within FVIII target levels with the DDAVP and FVIII concentrate combination treatment in the first 72 hours after the start of combination treatment, without adding off-...

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

Summary

ID

NL-OMON47474

Source
ToetsingOnline

Brief title
DAVID

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym
clotting factor VIII deficiency, Hemophilia A

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW,Ferring b.v.

Intervention

Keyword: DDAVP, Hemophilia A, non-severe, Pharmacokinetics, Surgery

Outcome measures

Primary outcome

The main endpoint will be the proportion of patients within FVIII target levels with DDAVP and FVIII concentrate combination treatment in the first 72 hours after start of combination treatment, without adding off-protocol FVIII concentrates.

Secondary outcome

1. A population based pharmacokinetic model

2. Number and nature of adverse events during combined treatment

3. Incidence & severity of bleeding

4. Incidence of thrombosis

5. Incidence and extent of tachyphylaxis

6. Economical evaluation

7. Experienced quality of care

Study description

Background summary

Hemophilia A is a rare x-linked hereditary bleeding disorder in which the secondary hemostasis is affected by a deficiency in clotting factor VIII (FVIII). As a consequence, patients may suffer from excessive bleeding in response to a minor trauma or injury. Treatment with FVIII concentrates is effective, but highly expensive. In non-severe hemophilia A patients, surgical procedures and bleedings are among the main reasons for treatment with FVIII concentrates. On average, treatment with FVIII concentrates costs ¤17,520 per non-severe hemophilia A patient, per surgical procedure. Moreover, high FVIII

dosages may cause the development of FVIII inhibitors with an incidence that is higher than recently conceived. Inhibitors are a major challenge in hemophilia A patients, as it renders administered FVIII concentrates ineffective, leading to more complications and increased mortality. Sometimes, endogenous FVIII is also inhibited by these inhibitors, leading to a severe hemophilia bleeding phenotype due to decrease in FVIII under 0.01 IU/ml. Therefore, it is of utmost importance to reduce administration of FVIII concentrates when not strictly indicated and when potential alternatives are available. The hypothesis of this study is, that the presence of limited to moderate amounts of endogenous FVIII in non-severe hemophilia A patients, may lead to broader therapeutic options in this patient category. More specifically, FVIII release can be stimulated by the on-market drug desmopressin (DDAVP). Endogenous plasma FVIII levels, temporarily increased by DDAVP, can be supplemented with FVIII concentrates in order to reach FVIII target levels.

Study objective

Primary objectives:
To assess the proportion of non-severe hemophilia A patients within FVIII target levels with the DDAVP and FVIII concentrate combination treatment in the first 72 hours after the start of combination treatment, without adding off-protocol FVIII concentrate.

Secondary objectives:
1. To acquire data to improve the population based PK-model for DDAVP and FVIII concentrate combination treatment in non-severe hemophilia A patients.
2. To establish (possible) adverse events of combination treatment; e,g, side effects of DDAVP, bleeding episodes, development of neutralizing antibodies, thrombotic events.
3. To establish the proportion of non-severe hemophilia A patients that reaches FVIII target levels with the DDAVP and FVIII concentrate combination treatment preoperatively and just after start of combination treatment.
4. To establish the amount of off-protocol FVIII concentrates required.
5. To evaluate the intra-individual reproducibility of DDAVP response.
6. To evaluate DDAVP tachyphylaxis and its extent.
7. To perform an economical evaluation to quantify the potential cost reduction of the combination treatment.
8. To evaluate the experienced quality of care in participating patients.

Study design

A multicenter observational non-randomized clinical trial

Study burden and risks

This study aims to evaluate the combination treatment with DDAVP and FVIII concentrate in non-severe hemophilia A patients in the perioperative setting and around bleeding. During combination treatment, we will measure FVIII plasma levels at least twice daily to guarantee safety, instead of once daily which is regular clinical practice in this setting.
Preoperative DDAVP-testing in each individual will be performed according to the DDAVP-testing protocol in each participating centre. During this procedure, a standard dose of DDAVP is infused and FVIII (and VWF) response is evaluated by measuring FVIII (and VWF) levels before and after DDAVP administration. Patients who have undergone a DDAVP-test already, with available test results, will not receive an additional DDAVP-test.

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

- Non-severe hemophilia A patients (FVIII equal to or higher than 0.01 IU/mL)
- In need of surgery or suffering from bleeding
- Age minimally 12 and maximally 70 years at study inclusion date
- Need for clotting factor concentrates; perioperatively, or around a bleeding
- Treatment duration with FVIII-concentrates of at least 48 hours
- Results of FVIII levels after a DDAVP test dose, or if test results are not available, willingness to undergo a DDAVP test
- Male gender
- (Parental) informed consent

Exclusion criteria

- Patients with other congenital or acquired hemostatic abnormalities
- Very low response to DDAVP after 1 hour * absolute increase in FVIII < 0.2 IU/mL
- Clinically relevant FVIII inhibiting antibodies (>0.5 BU) in medical history or preoperatively, unless successfully treated with immunotolerance therapy
- Start of FVIII-concentrate treatment >24 hours ago
- Contraindications for DDAVP, e.g. cardiovascular disease (see the protocol, appendix IV)
- Use of co-medication that has an interaction with DDAVP (see the protocol, appendix IV)
- Intolerance to previous DDAVP administrations
- DDAVP not advisable due to the type of surgery/bleeding according to the hematologist and/or surgeon

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-02-2017
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aafact
Generic name:	Factor VIII
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Advate
Generic name:	octocog alpha
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Helixate NexGen
Generic name:	octocog alpha
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kogenate
Generic name:	octocog alpha
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ReFacto AF
Generic name:	moroctocog alpha
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23569
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-005435-14-NL
CCMO	NL53686.078.15
OMON	NL-OMON23569