Implementation of pharmacokinetic-guided dosing of prophylaxis in hemophilia patients.

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To investigate the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B patients (predictive performance).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55874

Source
ToetsingOnline

Brief title
OPTI-CLOT: TARGET

Condition

- Blood and lymphatic system disorders congenital

Synonym
bleeding disorder, hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Clotting factor concentrate, Hemophilia, Pharmacokinetics, Prophylaxis

Outcome measures

Primary outcome

1. Observed FVIII and FIX levels in comparison to prospectively predicted FVIII and FIX levels by MAP Bayesian analysis (predictive performance).

Secondary outcome

1. Association of both prospectively and retrospectively collected real life- and simulated FVIII/FIX levels with bleeding episodes, daily activities and joint status.

2. Expectations, feasibility and experience with PK-guided dosing with the different factor concentrates (standard half-life versus extended half-life) as reported by patient/ caretakers and physician will be measured using a Visual Analogue Scale (VAS) at the start and end of the study.

3. Economic analysis in which costs and benefits of standard prophylactic treatment and PK-guided prophylaxis are compared.

4. Analysis of modifiers effecting PK parameters of FVIII/FIX concentrate in order to further optimize population PK models.

Study description

Background summary

Most severe and some moderate severe hemophilia patients receive prophylactic treatment with factor concentrate to prevent spontaneous bleeding in joints and muscles, decreasing the risk of arthropathy and long term disability.
Currently, initial dosing of prophylaxis is based on body weight and, often

hypothetically on maintenance of minimal factor VIII (FVIII) or factor IX (FIX) concentrate trough levels > 0.01 international units per milliliter (IU/mL) in both hemophilia A and hemophilia B. However, these trough levels are rarely measured, and dosing regimens are generally adjusted only when clinically relevant bleeding occurs, not taking microbleeds into account. Furthermore, it is well known that a large interindividual variability exists in the pharmacokinetics (PKs) of factor concentrates in patients. Therefore, besides an increased awareness of actual FVIII and FIX peak levels, PK-guided dosing of prophylaxis may lead to more optimal safeguarding of FVIII and FIX trough levels and may help achieve higher trough and peak levels when clinically indicated due to activity pattern. In addition, these levels may be achieved without increasing of the annual FVIII/ FIX concentrate consumption. Moreover, PK-guided dosing may provide support with regard to the introduction and dosing of novel extended half-life (EHL) concentrates. In all settings, cost and benefit of treatment should of course be taken into account. In this study, we hypothesize that FVIII/FIX trough and peak levels as set by treating physician can be predicted and achieved effectively by application of PK-guided prophylactic dosing.
To analyze this, hemophilia patients treated prophylactically will be enrolled in the study and categorized according to type of hemophilia (hemophilia A or hemophilia B) and type of concentrate (standard half-life (SHL) or EHL). Severe hemophilia patients (FVIII/ FIX<0.01 IU/mL) on prophylaxis will be analyzed separately from non-severe hemophilia patients on prophylaxis (FVIII/ FIX>=0.01 IU/mL).

Study objective

To investigate the reliability and feasibility of PK-guided prophylactic dosing of factor concentrates in hemophilia A and B patients (predictive performance).

Study design

Multicenter, non-randomized, prospective cohort study in hemophilia patients on SHL prophylaxes and in hemophilia patients switching to or on EHL prophylaxis. Frequency and timing, and dosing of administration will be based on constructed individual PK-profile.

In addition, in those cases where retrospective data of individual patients is available of administered factor concentrates and achieved FVIII/FIX levels, this will be utilized to enrich individual PK profiles and to fortify available population PK models (*real life data*).

Intervention

All patients will be treated with the same commercially available FVIII/

FIX-containing concentrate as they would be treated with during standard treatment. Patients will not switch products for study purposes.

PK-profiling:
All individuals will undergo individual PK-profiling according to study protocol, with infusion of specified dose of factor concentrate and set blood sampling time points depending on type of hemophilia and type of factor concentrate.
Doses will be calculated for the FVIII/ FIX target trough and peak values set by the treating physician, taking patient characteristics and activity pattern into account and in consultation with patient/ caretakers. In addition, a dosing regimen will be constructed for treatment of mild, severe and life-threatening bleedings according to the Dutch National Hemophilia Consensus and clinical experience.
Dosing regimens will generally be in accordance with the labels of the administered clotting factors. However in some cases higher doses may be applied. The latter however can be done safely as FVIII/FIX levels are monitored.

Initial PK-guided treatment (12 weeks):
Patients will be initially on PK-guided treatment for 12 weeks according to the constructed dosing regimen. A minimum of three blood sampling moments will be planned divided over twelve weeks.

Follow-up treatment under PK-guidance (24 weeks):
During last 24 weeks patients will be followed on PK-guided treatment during prophylaxis. At the end of this follow-up period, blood sampling will be performed.

MAP Bayesian analysis:
MAP Bayesian analysis will be applied to obtain the individual PK parameters on basis of the samples obtained from the pharmacokinetic profile. In MAP Bayesian analysis population PK characteristics are combined with observations (FVIII/FIX levels) from the studied individual to obtain the most probable values for its PK parameters. With the derived PK parameters the optimal dosing regimens can be derived producing adequate exposure. For most products population PK models are available from literature and will be programmed in NONMEM software. In cases where no population PK model is available to determine an individual PK profile, these will be constructed by treatment sampling, other sources and if necessary through negotiations with pharmaceutical company.

Study burden and risks

There are no additional risks compared to the standard treatment due to intensive monitoring of FVIII/FIX plasma levels. As it has been shown that patients are often dosed too high or too low, based on their body weight, it is

important to explore other ways of dosing (i.e. PK-guided dosing). This may enable better targeting of FVIII/FIX plasma levels, with a possible reduction of complications and reduction of costs by reducing the amount of factor concentrate used.

Individual PK-profiling will be in all study patients, which may be seen as an extra burden (hematoma or inconvenience due to failure of venipuncture). In young children and patients with impaired venous access, we will try to apply a intravenous catheter, to draw blood at different time points without having to do repeated punctures. In addition, validation of predicted dosing by extra blood sampling may also be seen as burden. However, these moments will be planned efficiently around intravenous infusion of SHL or EHL factor concentrates. To reduce burden of traveling for patients/ caretakers, blood sampling moments can be conducted at a patients* home or workplace if preferred and possible.

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)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Hemophilia A and B patients of all ages on prophylaxis;
- Prophylaxis with SHL factor concentrates or EHL factor concentrates;
- Written (parental) informed consent, according to local law and regulations

Exclusion criteria

- Patients with other congenital or acquired hemostatic abnormalities;
- General medical conditions which may interfere with participation in the study;
- Inability to adhere to prophylaxis and/ or inability to keep detailed logs on infusion and bleeding episodes;
- Withdrawal of (parental) informed consent.

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Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-07-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aafact
Generic name:	human coagulation factor VIII
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Advate
Generic name:	human coagulation factor VIII (rDNA), octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Helixate NexGen
Generic name:	human coagulation factor VIII, octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kogenate Bayer
Generic name:	human coagulation factor VIII, octocog alfa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ReFacto AF
Generic name:	human coagulation factor VIII, moroctocog alfa
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-05-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-11-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2024
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003869-33-NL
CCMO	NL67754.078.18