A Phase 3b Clinical Study To Assess Whether Regular Administration Of Advate In The Absence Of Immunological Danger Signals Reduces The Incidence Rate Of Inhibitors In Previously Untreated Patients With Hemophilia A

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Primary objective:Determine the incidence rate of inhibitor formation in PUPs with severe and moderately severe hemophilia A during the first 50 exposure days (EDs) to starting with a once weekly prophylactic regimen together with the minimization...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON35535

Source
ToetsingOnline

Brief title
Early Prophylaxis Immunologic Challenge (EPIC) Study

Condition

- Haematological disorders NEC

Synonym
Coagulation Factor VIII deficiency / Blood disease

Research involving

Human

Sponsors and support

Primary sponsor: Baxter
Source(s) of monetary or material Support: Commercial Sponsor

Intervention

Keyword: Advate, Hemophilia A

Outcome measures

Primary outcome

Incidence of inhibitor formation in severe and moderately severe hemophilia A (FVIII <= 2%) within the first 50 EDs to ADVATE (prior exposure to FVIII up to a maximum of 3 EDs but maximum 2 exposures per event - to any FVIII concentrate are allowed, and infusions for bleed management will be included in the 50-ED calculation)

Secondary outcome

• Incidence of inhibitor formation in severe hemophilia A (FVIII <= 1% within the first 50 EDs of ADVATE

• Time to inhibitor formation

• Incidence rate for low-titer, high-titer, transient, and all inhibitors

• Incidence of SAEs and non-serious AEs at least possibly related to ADVATE

• Number, type, and severity of all bleeds experienced (eg, intracranial hemorrhage, joint, soft tissue)

• Number, type, and severity of all bleeds experienced when different prophylactic dosing frequencies are used (once per week versus 2-3 times per week)

• Number and type of surgeries (which cannot be postponed until after 20 EDs)

• Association of known risk factors to inhibitor formation: FVIII gene mutation type, FVIII haplotype, HLA haplotypes, family history of inhibitors, infections, immunomodulatory gene polymorphisms (tumor necrosis factor-alpha [TNF-α], interleukin-10 [IL-10], cytotoxic Tlymphocyte antigen 4 [CTLA4])

• Total FVIII consumption (in international units [IU]) for each subject

• FVIII-specific antibody isotype for all subjects at study entry and every 10 ED

Study description

Background summary

The formation of neutralizing antibodies (inhibitors) against FVIII is the most serious disease-related complication of hemophilia A treatment, typically occurring in approximately 30% of severe PUPs. The highest risk of developing inhibitors to FVIII occurs during the first 20 exposure days (EDs). Of those patients who develop inhibitors, 50% of will develop inhibitors within the first 20 EDs and 95% during the first 50 EDs. Prophylactic factor replacement therapy is now an established approach to prevent severe joint bleeds and arthropathy.
Inhibitor development is a complex, multifactorial immune response involving both patient-specific and treatment-related factors. Of the known risk factors, intensive treatment at an early age has been shown to be significant, and clinical observations have suggested that early prophylaxis (ie, first exposure to FVIII in the absence of a bleed) may protect patients from inhibitor development with the goal to induce tolerance against FVIII.
One of the patient-specific factors predisposing to inhibitor development is severe defects in the FVIII gene, such as large deletions, inversions (most commonly intron inversion) and stop mutations. Such mutations mean that there is no endogenous FVIII production, and therefore the FVIII protein cannot be presented to the immune system to establish central immune tolerance. If such patients are then given a FVIII product, it is seen as a foreign protein by their immune systems.
Most prophylactic regimens use relatively high doses of FVIII, for example 50 IU/kg three times weekly, with treatment started at or just after the first significant joint bleed. This means that the FVIII antigen is being given at

high doses and at the same time when danger signals are present. This clinical study is based on the hypothesis that if such danger signals are prevented and low doses of FVIII are used, the risk of developing FVIII inhibitors can be decreased.

To date, no prospective study has been done to investigate whether regular, systematic exposure to low doses of FVIII during the first 50 EDs can reduce the risk of inhibitor formation. This study will determine if a low dose, early prophylaxis regimen starting with once weekly infusions can reduce the inhibitor incidence rate in severe and moderately severe hemophilia A patients.

Study objective

Primary objective:
Determine the incidence rate of inhibitor formation in PUPs with severe and moderately severe hemophilia A during the first 50 exposure days (EDs) to starting with a once weekly prophylactic regimen together with the minimization of immunological danger signals

Secondary objectives:
- Determine the general safety and efficacy during the first 50 EDs to ADVATE of an once weekly early prophylactic regimen starting once weekly in PUPs with severe and moderately severe hemophilia A
- Gather information about the temporal associations and molecular and cellular mechanisms involved in the development of an immune response to factor VIII (FVIII) during the first 50 EDs to ADVATE

Study design

This is a Phase 3b, prospective, historically controlled, single arm, international, multicenter study in PUPs with severe and moderately severe hemophilia A. The inhibitor incidence rate observed using this early prophylaxis regimen will be compared to that previously observed in historical cohorts, including the ADVATE PUP Study (Baxter study number 060103; historical control). The estimated number of study subjects is 100, and the estimated number of global study sites is approximately 75.

Intervention

ADVATE will be administered by intravenous infusion at a dose of 25±5 IU/kg once per week.
Additional on-demand ADVATE infusions (25-50 IU/kg) for bleeds should be administered as indicated. The maximum dose for any once weekly on-demand infusion will be 50 IU/kg.

Study burden and risks

It has been demonstrated in Phase 3/4 and post-authorization surveillance studies that ADVATE was safe and effective for the treatment and prevention of bleeding episodes in various settings and patient populations, including PUPs. Based on the available evidence, as described above, there are no additional risks anticipated other than those described in the IB.
This new prophylaxis regimen incorporates several factors:
• Low number of EDs before prophylaxis starts
• Low dose and low frequency regimen
• Young age at start of regimen
• Minimization of immunological danger signals
It has been shown in the pilot study and other studies, that starting prophylaxis at a young age does not increase the risk of inhibitor development. If prophylaxis is started earlier this may result in fewer joint bleeds and better joint scores, and thus a better outcome for the patient. Other benefits of the regimen would include the following:
• Central venous access device (CVAD) is not necessary because of once a week administration; this eliminates the need for a surgical procedure and prevents the associated cell damage and generation of danger signals.
• The dosing frequency and the dose can be increased if the initial dose is ineffective.
• Weekly dosing aids subject compliance: the best-case scenario is only one visit to the HTC required per week (in contrast to the normal 3 times weekly regimen)
• Lower doses, less frequent treatments, and the prevention of inhibitors offer pharmacoeconomic benefits.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Subjects with severe and moderately severe hemophilia A (FVIII <=2%)
• Certain FVIII mutation types (eg, large multi-domain deletions; nonsense mutations; insertions/deletions/inversions that result in a premature stop codon; intron 22 inversions) can be used to corroborate a severe hemophilia A phenotype when laboratory assays show FVIII levels >=1% because of rounding errors or carryover effect from a previous FVIII administration; a central laboratory FVIII assay is required to confirm subject eligibility
2. Subjects < 1 year of age
3. Subjects must have <=3 EDs to any FVIII concentrate or FVIII-containing product used for treatment of minor bleeds (bleeds requiring no more than 2 infusions per event), or for preventative or precautionary infusions following possible injury.
4. Subjects with prior circumcision are allowed to enroll only if bleeding issues related to circumcision were the cause for the original diagnosis of hemophilia A and no more than 2 EDs of FVIII treatment were required.
5. Adequate venous access (without need for CVAD-placement) as determined by the physician
6. Written informed consent from legally authorized representive(s)

Exclusion criteria

1. Life-threatening conditions (intracranial hemorrhage, severe trauma) or requirement for surgery at the time of enrollment
2. Evidence of inhibitor >=0.6 BU in Njimegen-modified Bethesda Assay at study start (samples may be retested using lupus-insensitive inhibitor tests to reduce the number of false positive inhibitor test results)
3. Inherited or acquired hemostatic defect other than hemophilia A
4. Any clinically significant, chronic disease other than hemophilia A
5. Known hypersensitivity to ADVATE or any of its constituents
6. Any planned elective surgery that cannot be postponed until after the first 20 EDs

7. Participation in the Hemophilia Inhibitor PUP Study (HIPS)
8. Application of red blood cell, platelet, or leukocyte concentrates, or plasma
9. Administration of any medication affecting coagulation or platelet function
10. Systemic administration of any immunomodulatory drug (eg, chemotherapy, intravenous glucocorticoids)
11. Participation in another clinical study involving an IP or device within 30 days prior to study enrollment or during the course of this study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2012
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ADVATE Antihemophilic Factor (recombinant), Plasma/Albumin-Free Method (rAHF-PFM), Octocog alfa
Generic name:	ADVATE (rAHF-PFM)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-12-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-09-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-000410-18-NL
CCMO	NL38458.091.11