Therapy of Refractory Inhibitors with immUne Modulation in Patients with Hemophilia. The TRIUMPH trial

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To evaluate the efficacy, safety and feasibility of combined immune modulation with rituximab, ITI and MSCs in terms of eradication of FVIII inhibitory activity in hemophilia A patients.

Ethical review	Not approved
Status	Will not start
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON42326

Source
ToetsingOnline

Brief title
TRIUMPH trial

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Immune disorders NEC

Synonym
Haemophilia A; FVIII deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Bayer HealthCare,Bedrijf

Intervention

Keyword: allo-antibodies, Haemophilia A, immune modulation, Mesenchymal Stem Cells

Outcome measures

Primary outcome

Primary objective is to evaluate the efficacy, safety and feasibility of

combined immune modulation with rituximab, ITI and MSCs in terms of eradication

of FVIII inhibitory activity in hemophilia A patients.

Secondary outcome

Secondary endpoints are to evaluate the immune changes during the TRIUMPH

protocol in terms of T-cell and B-cell proliferation and modulation, time to

Complete Response and Partial Response, time to Relapse and adverse events

Study description

Background summary

The hallmark of treatment of patients with hemophilia A is regular infusion with clotting factor concentrates. Currently, one of the biggest challenges in hemophilia A treatment in developed countries is the treatment after formation of allo-antibodies (inhibitors) against administered Factor VIII (FVIII), which happens in about 25% of the patients. These patients are treated with Immune Tolerance Induction (ITI) with a success rate of 70-85%. About 15-30% of patients is refractory to ITI and in another 15% relapses occur after initial inhibitor eradication. For these patients, no standard protocol is available for inhibitor eradication. In selected cases, rituximab is used in combination with ITI, but the long-term efficacy of this approach is only 10-15%. New treatment options are urgently needed for refractory inhibitor patients. We will evaluate the efficacy, feasibility and safety of the treatment of hemophilia A patients with refractory inhibitors using triple therapy with ITI, rituximab and Mesenchymal Stromal Cells (MSCs). We will characterize how this triple treatment affects the immune system and its response to administration of recombinant FVIII (rFVIII).

Study objective

To evaluate the efficacy, safety and feasibility of combined immune modulation with rituximab, ITI and MSCs in terms of eradication of FVIII inhibitory activity in hemophilia A patients.

Study design

Open-label, prospective, single centre, non-randomized prospective phase I/II study.

Intervention

Patients will be treated with rituximab, MSCs and rFVIII.

Study burden and risks

Burden consists of repetitive infusions of rituximab, MSCs and rFVIII, additional blood draws. Reported side effects of rituximab include infusion related reactions, infections and allergic reactions. For rFVIII this includes allergic reactions. Documented side effects of MSCs infusion has been limited to infusion reactions. So far no severe side effects have been reported concerning treatment with MSCs. Theoretical risks are infusion reaction, toxicity of DMSO, microbiological contamination of MSCs product leading to severe infections, ectopic tissue formation, tumorigenicity and graft-versus-host disease when allogeneic MSCs are used.
However, considering the life -threatening bleedings which can occur in these patients, we expect an overall benefit in terms of improved hemostasis.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Adult patients with mild, moderate or severe hemophilia A with a current anti-FVIII inhibitor that have failed previous regular ITI, independent of titre height.

Exclusion criteria

- Patients with active, severe or uncontrolled infection
- HIV positivity and/or CD4 < 400 mm3/ml
- Significant hepatic dysfunction (total bilirubin * 30 µmol/l or transaminases * 2.5x upper normal limit)
- Significant renal dysfunction requiring hemodialysis
- Intolerance of exogenous protein administration
- Currently participating in interventional hemophilia studies
- Known uncontrolled toxicity for DMSO
- Any psychological, familial, sociological and/or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Life expectancy <3 years
- History of active cancer during the past 5 years, except basal carcinoma of the skin

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO

Date:	10-12-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	28-12-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2014-000661-43-NL
CCMO	NL54758.000.15