Efficacy and Safety of human apotransferrin in patients with β-thalassemia intermedia

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To study the effect of apotransferrin administration in patients with β thalassemia intermedia on erythropoiesis as reflected by hemoglobin level or transfusion dependency. Secondary objectives are the effect of apotransferrin on the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON55838

Source
ToetsingOnline

Brief title
Apotransferrin in patients with β-thalassemia

Condition

- Red blood cell disorders
- Blood and lymphatic system disorders congenital

Synonym
beta-thalassemia, inherited anemia

Research involving
Human

Sponsors and support

Primary sponsor: Sanquin Plasma Products
Source(s) of monetary or material Support: Sanquin Plasma Products BV

Intervention

Keyword: beta-thalassemia, transferrin

Outcome measures

Primary outcome

The primary efficacy parameter is the haematological response defined as the change from baseline of haemoglobin level, expressed as mmol/L and percentage, in NTDβTI/TDβTI patients or change from baseline of the number of RBC units transfused/week in TDβ1TI patients.

Secondary outcome

Secondary parameters include an increase of > 0.9 mmol/l (1.5 g/dl) in Hb in NTDβTI and TDβTI (before transfusion) and a reduction of at least 50% of the number of Red Blood Cell (RBC) units transfused/week from baseline in TDβTI. The pharmacokinetics of transferrin in plasma and changes in iron metabolism as reflected by serum iron, NTBI and LPI levels, hepcidin, ferritin, sTfR and iron saturation will be studied. Oxidative stress will be assessed by plasma levels of advanced glycation end products (AGEs) and the lipid peroxidation product malondialdehyde (MDA). Moreover, the effect on markers of erythropoiesis like reticulocyte count, erythropoietin levels, red blood cell indices, and spleen size will be studied. All adverse events (number, type) will be analysed regarding to causality, seriousness, outcome and expectedness.

Study description

Background summary

Beta thalassemia is an inherited disorder characterized by the defective synthesis of β-globin chains. Patient with β thalassemia intermedia suffer from anemia due to ineffective erythropoiesis, chronic hemolysis and extramedullary erythropoiesis resulting in splenomegaly and iron overload. Treatment of Bbbth1/th1 mice, a mice model of β-thalassemia intermedia, with human apotransferrin markedly improved the disturbances in iron and red cell turnover characteristic for thalassemia. Apotransferrin normalized labile plasma iron concentrations, increased hepcidin expression, normalized red blood cell survival and increased hemoglobin production, and concomitantly decreased reticulocytosis, erythropoietin level and splenomegaly.

Study objective

To study the effect of apotransferrin administration in patients with β thalassemia intermedia on erythropoiesis as reflected by hemoglobin level or transfusion dependency. Secondary objectives are the effect of apotransferrin on the pharmacokinetics of transferrin plasma levels, iron metabolism, oxidative stress, and erythropoiesis. Moreover the safety of apotransferrin transfusion will be studied.

Study design

A phase II prospective, open-label, non-controlled, single-centre trial

Intervention

Patients will receive an intravenous dose of 340 mg/kg human apotransferrin every two weeks for 14 weeks (NTDβTI) or 16 weeks (TDβTI).

Study burden and risks

NTDβTI patients will receive an intravenous dose of human apotransferrin in the hospital every two weeks for 16 weeks. The patients will be followed after the last infusion until the transferrin levels are back to baseline (total study period 16 weeks + 1-3 weeks expected follow-up). The study period of NTDβTI patients will be prolonged by 4 weeks for two extra apotransferrin infusions. So total study period will be 18 weeks + 1-3 weeks expected follow-up. Several blood samples will be taken during the study. Prior each infusion and 2 weeks after the last infusion, blood samples are taken to determine clinical chemistry variables (including transferrin levels, serum iron, ferritin, MDA, AGEs) (1 x 5 ml) and haematology variables (1x 6 ml). Moreover, a sample (1x 3 ml) is taken to determine sTfR, NTBI, LPI, hepcidin-25 and erythroferrone). For erythropoietin 5 ml blood is taken at the start and 2 weeks after last infusion (*week 16*) (in NTDβTI patients only). Serum iron, transferrin, NTBI/LPI and erythroferrone will be monitored every 2 weeks till transferrin levels are back to baseline (starting *week 17* for NTDβTI patients and *week 19* for TDβTI

patients). After the third infusion (week 4) blood samples for pharmacokinetic analysis of transferrin (3.5 ml) are drawn 5 minutes and 2 hours after stopping the infusion, and subsequently on day 1, 4, 7, and 14. A pre-treatment serum and EDTA-plasma sample (3 ml each) before the first apotransferrin infusion will be stored at -70 ºC by Sanquin Diagnostic Services BV for possible future testing of virus infection.
Vital signs are measured before each infusion and directly after the infusion with apotransferrin. A MRI of the spleen (if present) is performed to determine the size at the start and end of the study.
Patients may have direct benefit from treatment with human apotransferrin. No safety concerns are expected since human apotransferrin is a normal constituent of the human plasma. Moreover, previous clinical studies showed that apotransferrin can be transfused in high doses without serious adverse drug reactions.

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

1. Non-transfusion dependent β-thalassemia intermedia, defined as patients with microcytic anaemia in combination with an elevated HbA2 (>2.5%) and a haemoglobin of <6.2 mmol/L, or transfusion dependent β-thalassemia treated with a regular transfusion schedule.
2. Age >=18 years.
3. Adequate renal and hepatic function tests as indicated by the following laboratory values:
• Serum creatinine <=1.0 mg/dl (<= 88.7 µmol/L); if serum creatinine >1.0 mg/dl (>88.7 µmol/L), then the glomerular filtration rate (GFR) must be >60 ml/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease equation where the predicted GFR (ml/min/1.73 m2) = 186 x (Serum Creatinine in mg/dl) -1.154 x (age in years) - 0.203 x (0.742 if patient is female) x (1.212 if patient is black)
NOTE: if serum creatinine is measured in µmol/L, recalculate it in mg/dl according to the equation: 1 mg/dl = 88.7 µmol/L) and used above mentioned formula.
• Aspartate aminotransferase (ASAT)/ alanine aminotransferase (ALAT) <=2.5 × ULN
• Alkaline phosphatase (AP) <= 2.5 × ULN
4. WHO performance 0, 1 or 2.
5. Signed informed consent.

Exclusion criteria

1. Known with allergic reactions against human plasma or plasma products.
2. Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease).
3. Cardiac dysfunction as defined by: myocardial infarction within the last 6 months of study entry, unstable angina, or unstable cardiac arrhythmias.
4. Pregnant or lactating females.
5. Known with IgA deficiency with anti-IgA antibodies

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-06-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Human Apotransferrin 50 g/l
Generic name:	Human Apotransferrin

Ethics review

Approved WMO

Date:	28-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	13-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	16-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-001936-12-NL
CCMO	NL68157.018.18

Study results

Date completed: 31-03-2022

Results posted: 17-03-2023

Summary results
Trial ended prematurely

First publication
10-03-2023