Proton pump inhibition for secondary hemochromatosis in hereditary anemia, a phase III placebo controlled randomized cross-over clinical trial.

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

Summary

ID

NL-OMON48585

Source
ToetsingOnline

Brief title
PPI in secondary hemochromatosis.

Condition

- Haematological disorders NEC

Synonym
Hemochromatosis, iron loading.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Beurs ZonMW Goed Gebruik Geneesmiddelen;aanvullende beurs Innovatiefonds Zorgverzekeraars

Intervention

Keyword: Anemia, Hemochromatosis, Iron, Proton pump inhibitor

Outcome measures

Primary outcome

The main endpoint of this study, which formed the basis for statistical power calculations, is the change in LIC from baseline measurements measured by MRI of the liver after one year of treatment with esomeprazole compared to the change in LIC from baseline during one year treatment with placebo. The LIC will be expressed in mg Fe/g dw after data analysis of the T2* and T1 images of the MRI.

Secondary outcome

1. Tolerability of esomeprazole: the incidence of side effect / adverse events will be monitored every 3 months during study visits. Measurement of vitamin B12, zinc and magnesium, T0, T12 and T24. Report of airway infections.

2. Quality of life: this will be assessed with EQ5D-forms, with time intervals of 3 months.

3. Cost-effectiveness analysis of esomeprazole in treatment of iron overload in hereditary anemia. This will be assessed by a prospective cost-effectiveness analysis. IMCQ and iPCQ questionnaires will be filled in with time intervals of 3 months.

4. Related changes in markers of iron metabolism:

a. Plasma hepcidin T0.

b. Serum ferritin T0, T12, T24.

5. Compliance to study drug

a. Plasma gastrin T0, T6, T12, T18, T24.

b. Counting of the capsules.

6. Need for chelation therapy

Study description

Background summary

The number one cause of years lived with anemia in Western Europe is hereditary anemia. The major cause of morbidity and mortality in patients with hereditary anemia not requiring chronic blood transfusion is iron overload caused by increased uptake from the gut. Iron overload and hereditary anemia are a growing, underestimated emerging health care problem. Many patients on iron chelation therapy, including deferasirox (currently the most frequently used iron chelating agent) experience side effects such as gastro-intestinal problems and less frequently renal or hepatic failure. Not including the economic costs and loss of quality of life caused by side effects of iron chelation, the cost of prescription alone amounted about 5 million euros in 2014 in the Netherlands. Dietary uptake of iron can be reduced by gastric acid reduction. Observational studies suggest that PPIs reduce iron uptake. In a recent randomized controlled trial in hereditary hemochromatosis PPIs diminished the needed number of phlebotomies. Although, results of this trial cannot be extrapolated completely to patients with hereditary anemia, this is a strong suggestion for effectiveness in patients with hereditary anemia*s and secondary hemosiderosis. A safer alternative for the iron chelators would make it possible to intervene earlier in these patients at lower costs. Especially in low-income regions of the world, PPIs could be a life saving and affordable alternative to prevent and treat iron loading.

Study objective

Primary Objective to show that PPIs compared to placebo are an effective treatment of secondary hemochromatosis in a relative large number of patients with hereditary anemia and mild iron overload.

Secondary Objectives:
To assess the safety and side effects of treatment with esomeprazole.
To assess quality of life during treatment with esomeprazole compared with

placebo.
To evaluate cost-effectiveness of esomeprazole in treatment of iron overload in hereditary anemia.
To assess the changes in *iron markers* during treatment with esomeprazole compared with placebo.
To assess the need for chelation therapy after one year of treatment with esomeprazole compared with placebo.
To assess the adherence to therapy in a real life setting.

Study design

Randomised placebo controlled trial with crossover design.

Intervention

12 months treatment with esomeprazole 40 mg twice daily, 12 months treatment with placebo twice dialy.

Study burden and risks

Follow-up visits, blood sampling and MRI planning are all according to current clinical guidelines. Extra blood (gastrin and hepcidin analysis) will be taken. Every 3 months three questionnairies will be filled in to assess quality of life and cost-effectiviness. Extent of the burden will be minimal on top of the standard treatment protocol, besides the daily intake of two capsules.
Safety of esomeprazole treatment is one of the most important outcomes of the study. We will monitor the side effects / adverse events every visit. Extra visits or contact moments will be planned if necessary in case of adverse events. Special attention should be paid to interactions with other drugs as outlined in paragraph 12.1.h of METC protocol.
In our opinion, the potential benefit of esomeprazole outweighs the possible risks of this trial. Currently the only treatment option for iron overload is iron chelation therapy with potential toxic effects and severe side effects. Esomeprazole is generally considered as a medicament with an excellent safety profile. Therefore we consider the possible risks for the patients as acceptable.

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

o Diagnosis of hereditary anemia: hemoglobinopathy (including all sickle cell syndromes and beta-thalassemia), sideroblastic anemia, congenital dyserythropoietic anemia or an erythrocyte enzyme deficiency.
o Hemoglobin before study inclusion <7.0 mmol/L
o Clinically stable and relevant iron overload defined as either one of:
- a baseline LIC measurement by MRI between 3 and 15 mg Fe/g without having received iron chelation 2 months prior to entering the study.
- OR a baseline LIC measurement by MRI between 3 and 15 mg Fe/g on stable chelation therapy (deferasirox, deferoxamine or deferiprone), with documented stable dosage the preceding 2 months and no expected dose reductions or increases the next two years.
o Aged more than 18 years and able to sign informed consent.
o Received less than 10 units of blood during the preceding 12 months.
o Is expected to receive less than 4 units fo blood during the following 12 months
o Is not splenectomized during the preceding 24 months.

Exclusion criteria

o Pregnancy.
o Liver cirrhosis.

o Heart failure.
o Severe cardiac iron overload defined as MRI T2* < 20 ms.
o Severe liver iron overload defined as MRI LIC > 15 mg Fe/g dw.
o Expected poor compliance.
o Currently taking PPI and not able to stop for personal or medical reasons.
o Patients that are being phlebotomized as treatment for iron overload.
o Current peptic ulcer disease, gastro-intestinal bleeding or other causes of blood loss.
o Contra-indication for esomeprazole use.
o Concomitant use of clopidogrel.
o Contra-indication for MRI.
o Received more than 4 units blood during one of the treatment periods of 12 months.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-03-2018
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Esomeprazole
Generic name:	Esomeprazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-02-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-02-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-04-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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: 25811
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-003777-34-NL
CCMO	NL63198.041.17

Study results

Date completed:	12-04-2021
Results posted:	06-12-2021
Actual enrolment:	30

First publication
01-01-1900