RESEARCH ARTICLE

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

Annelies van Vuren[1] | Jean Louis Kerkhoffs[2] | Saskia Schols[3] |
Anita Rijneveld[4] | Erfan Nur[5,6] | Dore Peereboom[7] | Yves Gandon[8] |
Paco Welsing[9] | Richard van Wijk[10] | Roger Schutgens[1] |
Wouter van Solinge[10] | Joannes Marx[11] | Tim Leiner[12,13] | Bart Biemond[5] |
Eduard van Beers[1]

[1]Center for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[2]Department of Hematology, HagaZiekenhuis, The Hague, The Netherlands

[3]Department of Hematology, Radboud university medical center, Nijmegen, The Netherlands

[4]Department of Hematology, Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands

[5]Department of Hematology, Amsterdam University Centers, University of Amsterdam, Amsterdam, The Netherlands

[6]Department of Blood Cell Research, Sanquin Research, Amsterdam, The Netherlands

[7]Contactgroep Pyruvaatkinasedeficiëntie, Stichting Zeldzame Bloedziekten, Medemblik, The Netherlands

[8]Department of Radiology, CHU Rennes, University of Rennes, Rennes, France

[9]Division of Internal Medicine and Dermatology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[10]Central Diagnostic Laboratory - Research, Division of Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[11]University Medical Center Utrecht, Utrecht, The Netherlands

[12]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[13]Department of Radiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Correspondence
Eduard van Beers, Center for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Huispost C01.425, Postbus 85500, Utrecht 3508 GA, The Netherlands.
Email: e.j.vanbeers-3@umcutrecht.nl

Abstract

Iron overload is a severe general complication of hereditary anemias. Treatment with iron chelators is hampered by important side-effects, high costs, and the lack of availability in many countries with a high prevalence of hereditary anemias. In this phase III randomized placebo-controlled trial, we assigned adults with non-transfusion-dependent hereditary anemias with mild-to-moderate iron overload to receive esomeprazole (at a dose of 40 mg twice daily) or placebo for 12 months in a cross-over design. The primary end point was change of liver iron content measured by MRI. A total of 30 participants were enrolled in the trial. Treatment with esomeprazole resulted in a statistically significant reduction in liver iron content that was 0.55 mg Fe/g dw larger than after treatment with placebo (95%CI [0.05 to 1.06]; $p = 0.03$). Median baseline liver iron content at the start of esomeprazole was 4.99

versus 4.49 mg Fe/g dw at start of placebo. Mean delta liver iron content after esomeprazole treatment was −0.57 (SD 1.20) versus −0.11 mg Fe/g dw (SD 0.75) after placebo treatment. Esomeprazole was well tolerated, reported adverse events were mild and none of the patients withdrew from the study due to side effects. In summary, esomeprazole resulted in a significant reduction in liver iron content when compared to placebo in a heterogeneous group of patients with non-transfusion-dependent hereditary anemias. From an international perspective this result can have major implications given the fact that proton pump inhibitors may frequently be the only realistic therapy for many patients without access to or not tolerating iron chelators.

1 | INTRODUCTION

Iron overload is a serious complication in patients with transfusion-dependent congenital anemias.[1] However, iron overload was also detected in 65% of a cohort of previously non-transfused patients with hereditary hemolytic anemia,[2] due to inappropriately low hepcidin levels resulting in excessive intestinal iron absorption in response to ineffective or stress erythropoiesis.[3–5] Upon erythropoietin stimulation, differentiating erythroblasts rapidly increase erythroferrone production, which downregulates hepcidin transcription.[5–9] The resulting elevated levels of total body iron lead to clearance of non-transferrin-bound iron by the liver,[10–13] culminating in iron overload and related pathology.[14,15]

In patients with non-transfusion-dependent thalassemia a liver iron content (LIC) threshold of 3–5 mg Fe/g dry weight (dw) was associated with a higher prevalence of iron-related morbidity, including vasculopathy, endocrine disturbances, and osseous complications.[16] In non-transfusion-dependent thalassemia LIC-values increase approximately 0.5 mg Fe/g dw per year already resulting in clinically relevant iron overload in adolescents.[17] Recommendations for monitoring and treatment of iron overload are incorporated in all current guidelines for management of hemoglobinopathies,[18–20] and other anemias.[21–24] Iron chelation is currently the only treatment modality of iron overload in anemic patients. Treatment-related toxicity (e.g. gastro-intestinal complaints and renal toxicity) is a concern in daily clinical practice, and treatment itself is expensive.

Dietary non-heme iron typically consists of ferric iron which needs to be reduced into ferrous iron for absorption. Ferrireductases present on enterocytes require a proton gradient, additionally protons are needed to solubilize dietary iron salts. Subsequently, proton pump inhibitors (PPIs) might inhibit both processes.[25,26] We hypothesize that treatment with PPIs reduces iron absorption and may limit iron-loading in patients with non-transfusion dependent hereditary anemia. A hint of such an effect was already provided by the Pyruvate Kinase Deficiency Natural History Study.[27,28] Iron overload was better managed in a subgroup with an iron-restricted diet, PPIs, and calcium citrate.[27–29] Moreover, PPIs have shown to be effective in the reduction of phlebotomy requirements in patients with hereditary hemochromatosis.[30,31]

We investigated the safety and efficacy of PPIs in prevention and treatment of iron overload in non-transfusion-dependent hereditary anemias.

2 | METHODS

2.1 | Trial design

The PPI Shine Again trial was a phase III double-blind, placebo-controlled, cross-over, multicenter trial designed to assess the efficacy and safety of esomeprazole in the treatment of mild-to-moderate iron overload in patients with hereditary anemia. The study was conducted at five clinical centers in the Netherlands, all were appointed as centers of expertise in hereditary anemia. The study included a one-year inclusion period, and was, upon enrollment, followed by two double-blind treatment phases in a cross-over design of 52 weeks each (Figure S1). The trial is registered in the Netherlands Trial Register (trialregister.nl): NL6659, PPI Shine Again (PPI in secondary hemochromatosis).

2.2 | Randomization and study procedures

Patients were randomly assigned to start with one of the two treatments. The randomization sequence was generated with blocks of four. The random allocation sequence was generated by the drug manufacturer and corresponded with the provided sequentially numbered bottles. Patients were allocated by means of a telephone call to the blinded coordinating investigator. Treatment assignment was stratified for use of iron chelation therapy. The participants, care givers, and those assessing outcomes were unaware of the group assignments.

Three-monthly laboratory assessments and yearly MRI of liver according to current standard-of-care were implemented in the study design. Extra study laboratory assessments included six-monthly gastrin levels and baseline hepcidin level (measured batch-wise after study close-out). Every three-monthly study visit included review of medication, check of compliance, report of side-effects and airway infections. Iron intake was assessed yearly with the IRONIC-FFQ questionnaire.[32] The full trial protocol is available in the *Supplemental Digital Content*.

2.3 | Participants

Eligible participants were adult patients (≥18 years old), with a confirmed diagnosis of hereditary anemia (hemoglobinopathy, sideroblastic anemia, congenital dyserythropoietic anemia, or erythrocyte enzyme deficiency), and had clinically stable mild-to-moderate iron overload defined as a baseline LIC between 3 and 15 mg Fe/g without iron chelation therapy 6 months prior to entering the study, or with documented stable dosage of iron chelation the preceding 2 months and no expected dose alterations, as no dose alterations were allowed during the trial. Patients who were undergoing regular red-cell transfusion therapy were not eligible. During the trial, participants were excluded if they had received >4 units of blood during one study period. All patients provided written informed consent before trial enrollment.

2.4 | Trial intervention

Participants received esomeprazole 40 mg and placebo capsules bidaily for 12 months in the randomized order, and were instructed to take one capsule 15–60 min before breakfast and dinner. Site investigators were allowed to end treatment for patients experiencing severe side effects. Temporarily cessation of the study drug, or exclusion from the study, was considered in cases of co-administration of medication with potential drug interactions. Drug interactions lowering plasma levels of esomeprazole were not considered as an exclusion criterion.

2.5 | Measurement

A combined MRI of liver and heart was performed at yearly intervals according to current clinical practice. In brief, the protocol consisted of dedicated liver and electrocardiographically triggered cardiac T2*-weighted sequences to assess liver and myocardial iron concentrations. All images were acquired on the same commercially available 1.5 Tesla MR imager using a predefined and previously validated imaging protocol. A detailed description of the MRI protocol, including a thorough description of the R2* method is available in the review paper by Henninger et al.[33] and on https://imagemed.univ-rennes1.fr/. Upon completion of the acquisition, images were sent to a dedicated workstation for further analysis using the MRQuantif web application. MRQuantif is a dedicated software package that can be used to quantify LIC from T2* MRI acquisitions.

2.6 | End points

Primary end point was the difference in change of LIC measured by MRI between esomeprazole and placebo treatment. The LIC was determined by two independent observers (YG/AV). Inter observer variability assessment was calculated by the intraclass correlation coefficient (ICC).[34] Secondary efficacy assessment included changes in serum ferritin values. Safety assessments included incidence of adverse events and abnormal clinical laboratory tests (serum vitamin B12, magnesium and zinc levels). Reported adverse events were graded according to the CTCAE v4.03 criteria.

2.7 | Trial oversight

The trial was centrally approved by the ethics committee of the University Medical Center Utrecht (Utrecht, NL) and approved by the Board of Directors of the participating centers. The trial was conducted according to Good Clinical Practice guidelines, defined by the International Conference of Harmonization. All participating centers signed confidentiality agreements with the sponsor regarding the data.

2.8 | Statistical analysis

We estimated that 20 patients would need to be enrolled to have approximately 80% power ($\beta = 0.20$) to detect a difference in change in LIC between treatments of 2.0 mg Fe/g dw, conform a previous trial with PPIs conducted in patients with hereditary hemochromatosis.[31] In the estimation a yearly expected increase in LIC without intervention of approximately 0.4 mg Fe/g dw was incorporated. Estimation of the standard deviation for the sample size calculation was based on the standard deviations reported by Taher et al.[17,35] Dropout was estimated to be relatively high due to unscheduled blood transfusions, surgery with blood loss or other complications. Inclusion of a minimum of eight additional patients was proposed to compensate for dropout and lack of compliance.

The main analysis consisted of an intention-to-treat analysis and per protocol analysis. In the per protocol analysis patients who failed to receive their allocated treatment, noncompliant patients or patients who dropped out of the study before completing both treatment periods were excluded. Noncompliance for the placebo period was defined as missing more than 20% of dosages based on pill counts or serum gastrin level within the reference range or less than 50% increase compared to baseline for the esomeprazole period.[36]

For the primary efficacy analysis, a linear mixed model was used with change in LIC as dependent variable, a random intercept at patient level and treatment as independent variable. Sex, iron chelator use, (period) baseline LIC, and randomized order of treatment were included as covariates. Continuous secondary outcomes were analyzed using the same approach. For safety parameters (serum vitamin B12, magnesium and zinc values) randomized order of treatment and iron chelator use were included as independent variables in the model. Calculations were performed using IBM SPSS Statistics version 26.0.0.1 (SPSS Inc., Chicago, IL).

3 | RESULTS

3.1 | Baseline characteristics of the patients

From March 2018 through April 2019, 30 patients were enrolled (Figure 1). Four treatment periods were excluded based on transfusion requirements (more than four units in one treatment period). The

FIGURE 1 Screening, Randomization, and Follow-up. Shown is the disposition of the trial participants. The intention-to-treat population compromised 30 patients who underwent randomization, to receive either esomeprazole followed by placebo, or placebo followed by esomeprazole. *The two treatment periods referred to were the two treatment phases of one patient, one placebo period, and one esomeprazole period. [†]One placebo period and one esomeprazole period were excluded. Tx based on transfusion requirements.
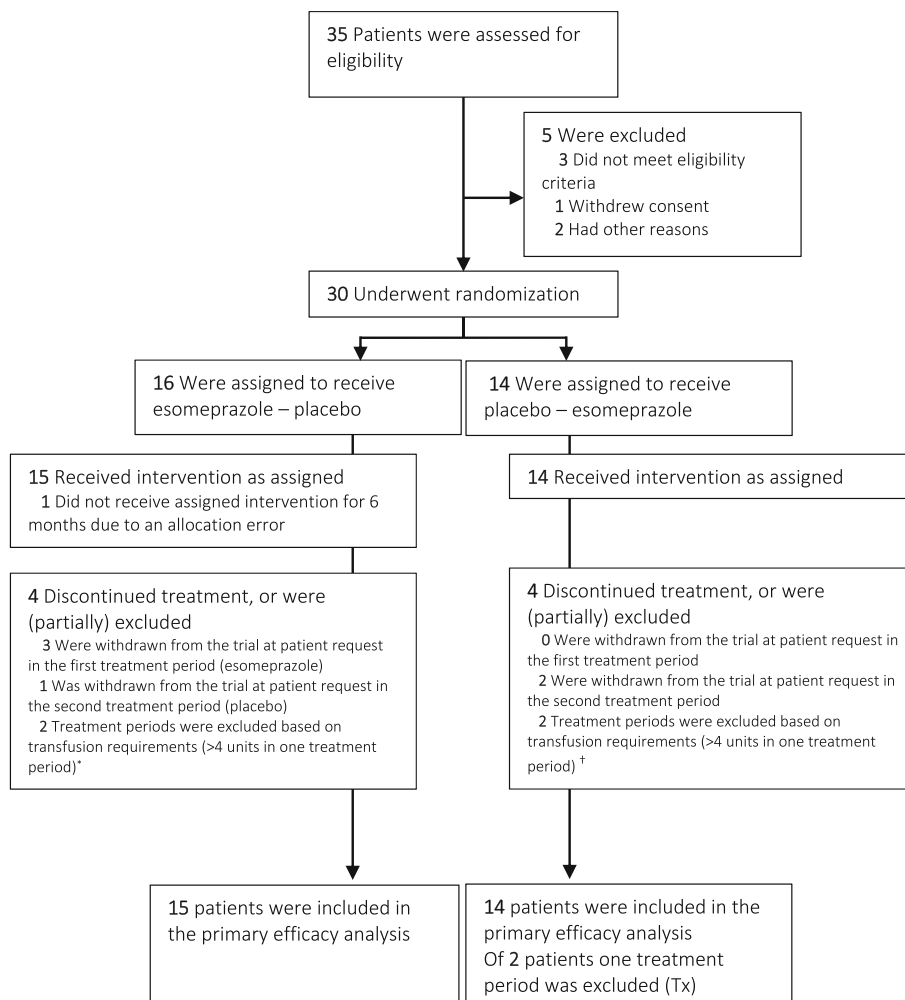
intention-to-treat population included all participants despite those excluded based on the set transfusion threshold. A total of six patients dropped out of the study at patient request of whom three completed the first treatment. Data assembled until dropout were included in the intention-to-treat analysis. Overall, data of 29 patients were included in the intention-to-treat analysis. As a consequence of drop-out, and one MRI not obtained according trial protocol, the analysis included 47 completed years of treatment (24 esomeprazole treatments and 23 placebo treatments). Baseline characteristics of the randomized population are provided in Table 1. The ICC representing reliability of the LIC-values was 0.996 (95% confidence interval [CI] [0.994; 0.997]). After central re-assessment at the end of the study baseline LIC-values were computed to be <3 mg Fe/g dw in five patients, >3–7 mg Fe/g dw in 18 patients and >7–15 mg Fe/g dw in 7 patients. Eleven patients were treated with a stable dose of deferasirox during trial participation (median dose per day 360 mg [range 180–1080 mg]).

3.2 | Primary endpoint

In the intention-to-treat analysis, we observed a significant effect of esomeprazole treatment: the reduction in LIC (delta LIC) was significantly greater after 1-year esomeprazole than after 1-year placebo (mean difference in LIC reduction 0.55 mg Fe/g dw; 95% CI [0.05 to 1.06]; $p = 0.03$) (Table 2, Figure S2). Median baseline LIC-value in the esomeprazole period was 4.99 mg Fe/g dw (IQR 3.47; 7.21) and in the placebo period 4.49 mg Fe/g dw (IQR 2.96; 6.35). Mean LIC reduction in the esomeprazole phase was 0.57 mg Fe/g dw (SD 1.20), compared to a reduction of 0.11 mg Fe/g dw (SD 0.75) in the placebo phase.

In 20 of the 47 completed treatment periods (43%) pill counts and/or gastrin values indicated therapy nonadherence. Per protocol analysis was performed in the subgroup with adequate adherence ($N = 26$ treatment periods). Results were in line with the intention-to-treat analysis with a mean difference in reduction of LIC of 0.51 mg Fe/g dw (95% CI [0.00 to 1.03]; $p = 0.05$).

A pre-planned modified efficacy analysis including baseline hepcidin/ferritin ratio provided proof for a relevant influence on treatment efficacy. Subsequently, patients were divided in two groups (hepcidin/ferritin ratio above group median, or below group median of 0.021). In patients with a low hepcidin/ferritin ratio treatment with esomeprazole resulted in a significant reduction in LIC of 1.30 mg Fe/g dw (95% CI [0.54 to 2.06]; $p = 0.003$) larger than placebo. After esomeprazole, there was a mean reduction of LIC of 1.20 mg Fe/g dw

Characteristic	Esomeprazole-placebo (N = 16)	Placebo-esomeprazole (N = 14)
Median age (range) – yr	47 (19; 66)	35 (23; 59)
Female sex – no. (%)	9 (56)	6 (43)
Median body mass index (range)	22.1 (17.8; 28.4)	21.5 (17.4; 30.0)
Diagnosis		
CSA	2	1
CDA	0	3
HE	1	0
NTDT	8	5
PKD	5	3
SCD	0	2
History of splenectomy (%)	5 (31)	2 (14)
History of cholecystectomy (%)	8 (50)	2 (14)
Iron chelation therapy (%)	6 (38)	5 (36)
Relevant other medicaments (%)		
Folic acid	11	10
Bisphosphonate or other therapy osteoporosis	2	2
ACE-inhibitor	0	1
Relevant co-morbidities		
Diabetes	1	0
Hypertension	1	0
Osteoporosis	2	0
Median number of blood transfusions in preceding 12 months (range)	0 (0; 9)	0 (0; 5)
Median iron intake		
Heme iron – mg per day	2.3 (1.8; 3.4)	1.4 (0.7; 2.8)
Non-heme iron – mg per day	5.2 (4.0; 8.5)	6.2 (4.9; 8.9)
Median number of phlebotomies in preceding 12 months (range)	0	0
Median markers of iron metabolism (IQR)		
Serum ferritin – µg/L	483 (302; 705)	603 (346; 807)
Serum transferrin saturation – %	59 (26; 81)	48 (31; 74)
Plasma hepcidin – µg/L	7.4 (4.2; 20.4)	11.3 (4.2; 17.7)
Median hemoglobin value (IQR) – g/dL	9.2 (7.9; 10.4)	9.7 (8.7; 10.2)
Median values of safety parameters (IQR)[a]		
Vitamin B12 – pmol/L	282 (199; 409)	275 (203; 500)
Magnesium – mmol/L	0.82 (0.81; 0.89)	0.83 (0.79; 0.88)
Median baseline LIC (IQR) – mg Fe/g dry liver weight	4.83 (3.13; 5.40)	5.44 (4.49; 8.37)

TABLE 1 Baseline demographic and disease characteristics. Data on all baseline demographics and disease characteristics are shown for all patients who underwent randomization. Characteristics are tabulated against treatment allocation.

Abbreviations: ACE, angiotensin converting enzyme; CDA, congenital dyserythropoietic anemia; CSA, congenital sideroblastic anemia; DFX, deferasirox; HE, hereditary elliptocytosis; IQR, interquartile range; LIC, liver iron content; NTDT, non-transfusion-dependent thalassemia; PKD, pyruvate kinase deficiency; SCD, sickle cell disease.

[a]Baseline zinc values are not presented in this table, as reference values (and assays) differed among participating centers. See *results section* for delta zinc values along the trial.

TABLE 2 Change in levels of liver iron content and iron parameters.

	Esomeprazole mean (SD)		Placebo mean (SD)		Effect esomeprazole[a] estimate (95% confidence interval)
Primary endpoint					
Δ LIC – mg Fe/g dw	N = 24	−0.57 (1.20)	N = 23	−0.11 (0.75)	−0.55 (−1.06 to −0.05)
Secondary endpoints					
Δ Ferritin – μg/L	N = 20	−18 (170)	N = 23	18 (135)	−23 (−121 to 76)
Δ Transferrin saturation – %	N = 22	−1.1 (18.4)	N = 23	6.7 (15.9)	−7.7% (−18.8 to 3.5)

Abbreviations: Δ, delta; LIC, liver iron content; SD, standard deviation.
[a]Effect estimate of esomeprazole as calculated by linear mixed model analysis with random intercept and treatment as independent variable. Sex, iron chelator use, baseline LIC and order were included as covariates.

(SD 1.32) versus an increase of 0.08 mg Fe/g dw (SD 0.76) after placebo. In patients with a high hepcidin/ferritin ratio esomeprazole led to a nonsignificant increase in LIC of 0.21 mg Fe/g dw (95% CI [−0.39 to 0.81]; $p = 0.47$) greater than placebo. After esomeprazole treatment, there was a mean increase in LIC of 0.06 mg Fe/g dw (SD 0.63) versus a reduction of 0.28 mg Fe/g dw (SD 0.73) after placebo treatment.

Iron intake was quantified with the IRONIC-FFQ questionnaire at baseline and after each treatment period. Changes in iron (heme or non-heme) intake were negligible over time (resp. $p = 0.81$, and $p = 0.84$). Four patients received red cell transfusions in the esomeprazole period and 2 patients in the placebo period.

3.3 | Key secondary end points

The change of serum ferritin was included as secondary end point; adhoc analysis of change in serum transferrin saturation was performed (Table 2, Figure S2). The difference in change in serum ferritin and transferrin saturation was nonsignificant when comparing esomeprazole and placebo (respectively −23 μg/L; 95% CI [−121 to 76]; $p = 0.65$, and −7.7%; 95% CI [−18.8 to 3.5%]; $p = 0.17$) (Table 2, Figure S2). Baseline ferritin levels and transferrin saturation levels were respectively 470 μg/L (IQR 306; 615) and 78% (IQR 39; 84) in the esomeprazole period and 455 μg/L (IQR 288; 694) and 54% (IQR 34; 81) in the placebo period. After esomeprazole treatment there was a decrease of 18 μg/L (SD 170) in serum ferritin, and a decrease of −1.1% (SD 18.4) in serum transferrin saturation. After placebo treatment, there was an increase in serum ferritin of 18 μg/L (SD 135) and an increase of 6.7% (SD 15.9) in serum transferrin saturation.

3.4 | Safety

Treatment periods of all patients exposed to esomeprazole or placebo were included in the safety analysis (N = 56). Most frequently reported adverse events were gastro-intestinal complaints, in particular in the esomeprazole-treated population. Adverse events occurring in over 10% of patients or graded grade 3 or higher are presented in Table 3. In one patient mild gastro-intestinal complaints (grade 2) led

TABLE 3 Adverse events occurring in at least 10% of patients or graded grade 3 or higher.

Event – no. (%)	Esomeprazole (N = 30)	Placebo (N = 26)
General disorder or administration-site condition		
Malaise	3 (10)	1 (4)
Fatigue	1 (3)	2 (8)
Gastro-intestinal disorder		
Nausea	1 (3)	3 (12)
Gastric pain or pyrosis	1 (3)	2 (8)
Diarrhea	6[a] (20)	2 (8)
Abdominal pain[b]	3 (10)	0 (0)
Infection or infestation		
Upper respiratory tract infection[c]	17	23
Lower respiratory tract infection[b,c]	3	4
Prosthetic valve endocarditis[b]	1 (3)	1 (4)
Sepsis eci[b]	0 (0)	1 (4)
Cholecystitis[b]	1 (3)	0 (0)
Flue (nos)	2 (7)	1 (4)
(Cardio)vascular disorder		
Vaso-occlusive crisis[b,c]	1	7
Rectus hematoma[b]	1 (3)	0 (0)
Kidney failure	0 (0)	1[a] (4)
Musculoskeletal or connective-tissue disorder		
Backpain	1[a] (3)	0 (0)

Note: Three grade 3 adverse events were reported (rapid decline in kidney function [placebo]; diarrhea in a patient diagnosed with colitis ulcerosa [esomeprazole], and severe backpain [esomeprazole]).
[a]One episode was graded grade 3 or higher.
[b]At least one serious adverse event occurred (hospitalization).
[c]Reported (number) is number of episodes.

to dose reduction of the study medicament (one capsule once daily), none of the patients discontinued trial participation due to adverse events. The majority of adverse events were graded 1 or 2.

Fourteen serious adverse events occurred, all concerning hospitalization due to various reasons. All serious adverse events were judged by the investigators to be unrelated to esomeprazole or placebo. None of the participants discontinued treatment, and no dose reductions were required.

Respiratory tract infections were reported separately. Three patients were prescribed antibiotics for respiratory tract infections in the esomeprazole period and 2 patients in the placebo period.

None of the participants was prescribed vitamin B12, magnesium or zinc supplementation during trial participation as a consequence of decreasing serum levels during the trial. Delta vitamin B12, magnesium or zinc values did not differ significantly between treatments.

4 | DISCUSSION

In this phase III, trial involving patients with non-transfusion-dependent anemias complicated by mild-to-severe iron overload esomeprazole 40 mg twice daily resulted in a significantly larger reduction in liver iron load of 0.55 mg Fe/g dw as compared to placebo after 1 year of treatment. We consider this difference clinically relevant given the average iron loading per year of 0.5 mg Fe/g dw in patients with non-transfusion-dependent thalassemia as observed previously.[17] Low individual hepcidin/ferritin ratio was an important predictor for treatment efficacy. Moreover, we established the safety of esomeprazole treatment for this specific indication, esomeprazole was associated with mainly low-grade adverse events.

The cross-over design of our study enabled us to include a heterogeneous group of anemias, which can be considered both a strength and a weakness of the trial. The underlying mechanism of iron loading is similar among these diseases, despite major differences in pathophysiology. Unfortunately, the low number of patients included per disease was too small to allow separate (sensitivity) subgroup analyses. Potency to accumulate iron in the absence of transfusions in SCD is subject of debate, however, there is a subgroup of SCD patients with extremely low hepcidin/ferritin ratios who may be at risk of iron overload via this route.[37]

We chose to dose esomeprazole twice daily to attain 24-h gastric acid suppression. Pharmacokinetic data of esomeprazole showed that 40 mg once daily attained pH ≥4 in 92% and 56% of patients for a minimal duration of respectively 12 and 16 h per day.[38] It is not known yet whether once daily dosing may also result in a relevant effect, given the fact that food is predominantly ingested during daytime. We strongly advice to address this question in future studies, as therapy adherence was poor for a twice daily regimen.

Five patients met the inclusion criteria (MRI conform standard care LIC ≥3 mg Fe/g dw), but during the blinded centralized reassessment at the end of the trial LIC-values appeared to be slightly lower. This may have had an effect on the average decrease in LIC, as previous trials with deferasirox reported larger decreases in LIC in patients with higher baseline LIC.[17,35,39] It would be recommendable to specifically study the (added) efficacy of PPI therapy (to iron chelators) in patients with more severe iron load (LIC ≥7 mg Fe/g dw), a group that was underrepresented in our trial.

In many countries, PPIs are currently readily available as over-the-counter drugs, also in low-resource countries. Adverse events are infrequent and generally mild. However, there is a growing concern regarding rare potentially severe side effects including (severe) enteric infections, cardiovascular diseases, pneumonia, hypomagnesemia, acute interstitial nephritis, vitamin B12-deficiency, dementia, and osteoporosis, resulting from chronic use of PPIs. For most of these side effects, it is uncertain if the association is based on causality as their incidences are mainly based on observational studies.[40,41] Likewise, long-term use of PPIs was associated with increased risk of gastric cancer.[42,43] Contrasting, extended PPI-use for indications that were not previously related to gastric cancer development PPI-use over 5 years was associated with a decreased risk.[43] Awaiting prospective trials that investigate the absolute risks of long-term PPI treatment on severe complications, these associations should not withhold consideration to use this treatment in patients with a clear indication.

Deferasirox is currently the treatment-of-choice in patients with iron overload. The THALASSA trial reported a LIC reduction of 1.95 mg Fe/g dw in the 5 mg/kg group after 1 year from a median baseline LIC-value of 11.7 mg Fe/g dw. LIC reductions were larger in patients with higher baseline LIC-values.[17] Similarly, the THETIS trial reported the smallest LIC reduction (1.82 mg Fe/g dw) in patients with LIC 5- ≤ 7 mg Fe/g dw with a mean dose of 8.95 mg/kg.[39] Compared with these results, deferasirox is likely to be more potent than esomeprazole in reduction of LIC in mild-to-moderate iron overload. However, this does not preclude implementation of PPI-therapy in treatment schedules for iron overload in patients with non-transfusion-dependent hereditary anemias, particularly in those patients with low hepcidin/ferritin ratios. Accounting its favorable safety profile and low costs, PPIs may be considered as an interesting therapeutic option to treat but also to prevent progression of iron overload and thereby the need for treatment with iron chelators in patients with mild iron overload (LIC ≥3–5 mg Fe/g dw). In case of more severe iron overload (LIC ≥5 mg Fe/g dw) we suggest to consider addition of PPI-therapy to iron chelators. From an international perspective this positive result may have major implications, as in certain areas of the world the prevalence of hereditary anemia is much higher,[44] but availability of iron chelators much lower. In these areas, PPIs may be the only realistic treatment option for many patients.

In conclusion, high-dose one-year esomeprazole treatment induced a significantly larger reduction in LIC when compared to placebo in patients with mild-to-moderate iron overload due to non-transfusion-dependent hereditary anemias. Longer follow-up is needed to see whether this effect will last for a longer period.

AUTHOR CONTRIBUTIONS

ORCID

Annelies van Vuren https://orcid.org/0000-0002-4258-3836
Jean Louis Kerkhoffs https://orcid.org/0000-0001-5107-047X
Saskia Schols https://orcid.org/0000-0003-2423-2829
Erfan Nur https://orcid.org/0000-0002-7069-930X
Yves Gandon https://orcid.org/0000-0002-7729-6087
Paco Welsing https://orcid.org/0000-0003-2361-2803
Richard van Wijk https://orcid.org/0000-0002-8236-8292
Roger Schutgens https://orcid.org/0000-0002-2762-6033
Wouter van Solinge https://orcid.org/0000-0003-2867-2581
Tim Leiner https://orcid.org/0000-0003-1885-5499
Bart Biemond https://orcid.org/0000-0002-3199-7718
Eduard van Beers https://orcid.org/0000-0002-3934-7189

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