Gastroenterology 2017;153:678–680

BRIEF REPORTS

Proton Pump Inhibitors Decrease Phlebotomy Need in HFE Hemochromatosis: Double-Blind Randomized Placebo-Controlled Trial

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Phlebotomy constitutes the established treatment for HFE-related hemochromatosis. Retrospective studies have suggested proton pump inhibitors (PPIs) reduce the need for phlebotomy in this population. We conducted a randomized controlled trial to prove this. Thirty p.C282Y homozygous patients were randomly allocated to PPI (pantoprazole 40 mg/day) or placebo for 12 months. Phlebotomies were performed when serum ferritin was > 100 μg/L. Phlebotomy need turned out to be significantly lower in patients taking PPI ($P = .0052$). PPI treatment significantly reduces the need for phlebotomies in p.C282Y homozygous patients. In view of the known long-term safety profile of PPI, they can be a valuable addition to standard therapy. Clinicaltrials.gov: NCT01524757.

Keywords: Hereditary Hemochromatosis; Proton Pump Inhibitors; Randomized Clinical Trial.

Hereditary hemochromatosis (HH) is a disorder of iron homeostasis related to mutations in the HFE gene. The most common pathogenic mutations in the HFE gene are p.C282Y and p.H63D. The inheritance is autosomal recessive and the prevalence of p.C282Y homozygosity is 1 in 200 to 1 in 400 persons of Northern European descent.[1–3] Homozygous individuals may remain asymptomatic and have a normal quality of life. Iron accumulation can nevertheless cause severe organ damage, resulting in liver dysfunction (fibrosis, cirrhosis, hepatocellular carcinoma), arthropathy, and diabetes mellitus[4] with impact on quality of life and survival. Complications and symptoms can be prevented or regress by reducing the body's iron overload.

Established treatments to achieve iron depletion are phlebotomy, erythrocytapheresis, and iron chelation. By far the most commonly applied treatment is phlebotomy. Phlebotomy is performed every week or fortnight during the depletion phase and, on average, once every 3 to 6 months during the maintenance phase.[5] With each phlebotomy, about 500 mL of total blood, corresponding to roughly 250 mg of iron, is removed.

Side effects of phlebotomy (fatigue, fainting, loss of appetite) are experienced by 52% of patients in the induction phase and by 37% in the maintenance phase.[6] Therefore, alternative treatments are warranted.

Two publications report on the effect of the proton pump inhibitor (PPI) in patients with HH. An observational study reported a reduction from 5 to 1 phlebotomy per year in 7 p.C282Y homozygous HH patients receiving PPI treatment.[7] A recent retrospective study confirmed the significant reduction in phlebotomies from a median of 3.17 before PPI treatment to 0.5 per year with PPI in 57 p.C282Y homozygous HH patients.[8]

These 2 observational, non-randomized studies suggest that HH patients on PPI require fewer phlebotomies. To confirm these potentially important observations, we initiated a prospective, randomized, double-blind, placebo-controlled study in homozygous p.C282Y HH patients. We hypothesized that the use of PPI would significantly reduce the need for phlebotomies.

Fifteen patients were assigned to each group. Compliance in both groups was comparable with an average of >90% drug intake. Baseline demographics and clinical characteristics of the included patients are detailed in Table 1 (see also Supplementary Materials: Study Design).

A total of 31 patients were randomly enrolled either to the placebo or PPI (pantoprazole, 40 mg/day) group. One patient terminated the study after 2 months because of a facial rash (placebo group). The data of this patient were not included in the final results. One patient withdrew from the study because of fatigue after 10 months (PPI group). The results of this patient were included until withdrawal.

Abbreviations used in this paper: HH, hereditary hemochromatosis; PPI, proton pump inhibitor; SF, serum ferritin.

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2017.06.006

EDITOR'S NOTES

BACKGROUND AND CONTEXT

Phlebotomy is the established treatment to decrease iron accumulation in hereditary hemochromatosis patients.

NEW FINDINGS

Phlebotomy need significantly decreases when C282Y homozygous hemochromatosis patients start taking proton pump inhibitors (pantoprazole 40mg per day).

LIMITATIONS

This randomized controlled trial included thirty patients (15 treated, 15 controls).

IMPACT

Proton Pump inhibitors can be used as add-on therapy to reduce phlebotomy burden and iron accumulation in C282Y homozygous haemochromatosis patients.

At diagnosis, the HH patients had an average serum ferritin (SF) level of 1414 ± 867 μg/L (mean ± SD). Complaints at inclusion were fatigue in 44.8% (13/29), joint complaints in 53.3% (16/30), and sexual dysfunction in 36% (9/25).

There was no significant difference between the 2 groups for age, either at diagnosis or at start of the study, and also for the number of phlebotomies needed per year before the start of the study (Table 1). However, a significant difference ($P = .0052$) was measured in the total number of phlebotomies needed during the study period (Table 1; Figure 1). Patient 9 (placebo) did not need any phlebotomy during the study period, however required six phlebotomies before the study (four, 2 years prior to the study and two more 1 year prior).

Table 1. Patient Characteristics and Clinical Outcome Parameters

	Placebo (n=15)	PPI (n=15)	*P*-value
Age (*years as mean with SD*)			
At diagnosis	47.13 (± 11.04)	50.13 (± 8.86)	.2
Start of study	53 (± 10.5)	57.53 (± 6.51)	.49
Sex			
Male	12 (80%)	10 (67%)	
BMI	27.8 (± 3.39)	27.05 (± 4.37)	.3
Phlebotomies			
Year before study	4.87 (± 1.60)	5.33 (± 1.63)	.21
During study time	2.60 (± 1.55)	1.27 (± 1.03)	**.0052**
Ferritin level (*U/L*)			
0 mos	57.53 (± 10.02)	74.40 (± 27.55)	**.039**
6 mos	87.80 (± 19.25)	81.73 (± 24.54)	.22
12 mos	125.80 (± 37.06)	90.53 (± 46.18)	**.0145**
Transferrin saturation (%)			
0 mos	51.13 (± 17.01)	42.40 (± 16.40)	.082
6 mos	62.93 (± 17.68)	50.79 (± 19.01)	**.043**
12 mos	61.79 (± 17.94)	55.23 (± 24.15)	.217
Gastrin level (*pg/mL*)			
0 mos	36.47 (± 24.15)	56.13 (± 73.74)	.170
12 mos	32.73 (± 17.91)[a]	96.64 (± 71)[a]	**.0071**

NOTE. Serum ferritin level at inclusion was set between 50–100 μg/L; there was a slight deviation in 33% (39–138 μg/L) of the patients. Bold values indicate statistical significance.
Abbreviation: BMI, body mass index; PPI proton pump inhibitor.
[a]13 patients.

No serious side effects were registered. One patient (PPI) experienced diarrhea for 3 days because of a Campylobacter infection. The patient described more fatigue at the end of the study. Two patients (placebo) experienced an unpleasant feeling in the stomach. One patient (placebo) was more fatigued after the 12 months' study time. Increasing arthralgia was described in 3 patients (2 placebo, 1 PPI) (See Supplementary Materials: Side Effects).

One patient (PPI) withdrew after 10 months because of fatigue, 1 patient (placebo) had transient increased liver tests during an episode of viral upper respiratory infection, and 1 patient (PPI) had increased liver tests confirmed to be steatohepatitis.

Iron and Biochemical Variables

Although the SF level in the PPI group turned out to be significantly higher at the start (randomization was not based on SF levels), this group reached a significantly lower SF level after the 12 months of treatment ($P = .0145$), despite a significantly lower number of phlebotomies (Table 1). The serum gastrin levels were significantly higher in the PPI group at the end of the study period, consistent with the use of PPI. Transaminase levels and vitamin B12 levels did not change significantly (data not shown).

The daily use of PPI significantly reduced the number of phlebotomies needed to keep the ferritin level < 100 μg/L in HH patients homozygous for p.C282Y. This is the first randomized controlled trial with PPI in HH patients to demonstrate that effect. This study confirms the results of the observational, retrospective studies by Hutchinson and van Aerts.[7,8]

An important concern in long-term treatment with PPI is the development of side effects.[9] In our study, no serious adverse events were encountered during the 1-year study period. Freedberg et al[10] stated in their recent review that the list of potential adverse effects associated with PPI use is long, but the absolute risk increase is modest and the quality of evidence is low to very low.

Our study shows a few limitations. The number of included patients (n = 30) was lower than the number based on the power calculation previous to initiation (ie, 48). There was a stagnation of inclusions at 31, mostly because of the stringent inclusion and exclusion criteria (eg, PPI use). However, the number of patients that participated proved sufficiently large enough to achieve significance, as the measured PPI effect exceeded the effect we projected. The consumption of tea was not recorded before and during the trial.[11]

This randomized controlled trial proves that a significant reduction in phlebotomy need in p.C282Y homozygous hemochromatosis patients can be achieved by treatment with PPI. The results of this study open the way to individualize

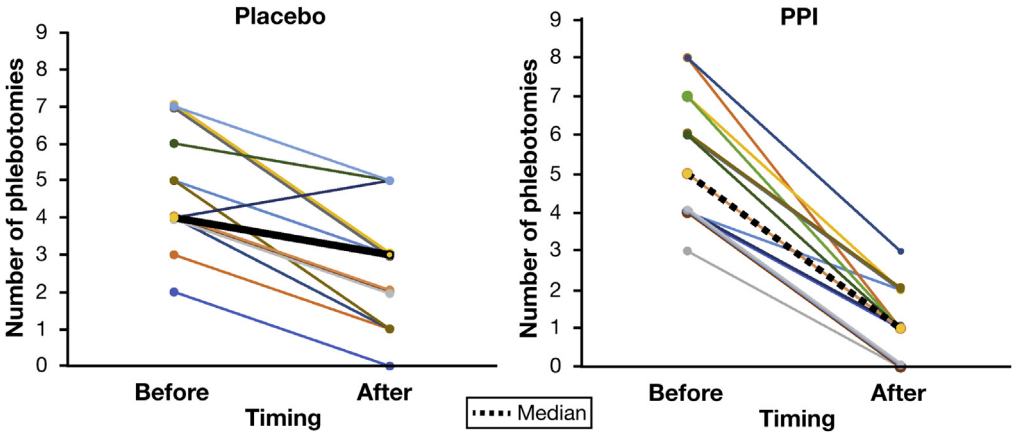

Figure 1. Total number of phlebotomies during the 12 months before the trial and during the 12 months of the trial.

treatment for p.C282Y homozygous patients. Future research must unravel the mechanisms that will help to target PPI therapy more precisely. Studies should focus on the minimal effective dose, long-term side effects, quality of life, and cost.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2017.06.006.

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Received April 3, 2017. Accepted June 7, 2017.

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Acknowledgments
D.C. is a fundamental clinical researcher for FWO-Vlaanderen.

Conflicts of interest
G.K. received financial support by the Sint-Annadal Foundation, Maastricht, The Netherlands. The Proton pump inhibitors and placebos were a kind gift from Takeda GmbH, Plant Oranienburg, Germany. The remaining authors disclose no conflict.

Supplementary Materials

Study Design

A randomized double-blind placebo-controlled trial was performed, during a trial period of 12 months, with pantoprazol 40 mg as the PPI. Via computer-generated randomization, the hospital pharmacist randomized, by block size of 6, patients to the placebo or PPI groups. The code was kept at the pharmacy of both participating hospitals. All tablets, PPI as well as placebo, were manufactured by Takeda GmbH (Plant Oranienburg, Germany) and had the same appearance and taste. PPIs and placebos were delivered in bulk, repackaged, and labeled. Study participants as well as involved researchers were blinded during the entire study. At the end of the study, the randomization code was provided by the hospital pharmacist to the care providers via e-mail.

After randomization, patients underwent routine laboratory evaluation with liver enzymes: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyltransferase, serum magnesium level, iron, transferrin, and transferrin saturation. Hematologic parameters measured were hemoglobin, white blood cell count, and platelets, at baseline and every 6 months. Vitamin B12 and gastrin concentrations were measured at baseline and at 12 months of treatment. Serum ferritin (SF) level was measured at baseline and every 2 months using the ElectroChemiLuminescense Immuno Assay (ECLIA; sandwich assay) of Roche Diagnostics. If the SF was > 100 μg/L, a phlebotomy of 500 mL whole blood was performed.

Study Participants

Inclusion and exclusion criteria are presented in Supplementary Table 1. If an indication to start PPIs would arise during the study period, the patient was planned to be withdrawn from the study.

Participants were included from September 2013 through July 2014. The study ended in July 2015, when the last patient ended the 12-month study period. All participants gave written informed consent. Study participants received their medication from their physician and compliance was measured by counting the number of returned tablets. Compliance was calculated by counting the days between two visits and the returned PPI/placebo tablets.

The sample size was calculated with a power of 90% and α of 0.05 for a pre-specified relevant reduction in number of yearly phlebotomies from 5 to 2 (standard deviation $= 3$), the calculated number of patients to be included was 48. In total, 31 patients entered the trial.

Patient Involvement

Before starting the study, patients were informed about the design of the study during the presentation of patient days organized by 2 patient's organizations (Hemochromatose Vereniging Nederland, the Netherlands and Haemochromatose Vereniging Vlaanderen, Belgium). Before randomization, all assessments were discussed with the patients in a face-to-face meeting. Patients who were involved in the study were informed personally about the results of themselves and of the entire study. During and after the study, we thanked the patients for their interest and involvement.

Study Setting

The study protocol was compliant with the ethical guidelines of the 1975 Declaration of Helsinki. Two hospitals were involved: the Zuyderland Medical Center in Heerlen, The Netherlands and the University Hospital Leuven (UHL), Gasthuisberg, Belgium. This study was registered in a public register (NCT01524757) and approval from both ethical committees was received (UHL: EudraCT Number 2012-000603-32; ML9419 – Zuyderland Medical Center in Heerlen: NL33544.096.12, METC 12-T-04).

Statistical Analysis

Statistical analyses were performed by using R-studio.[15] A two-tailed independent sample t-test was used to verify whether the means of continuous measurements were the same in the 2 independent groups. A P-value $\leq .05$ was considered significant.

Data from the 2 different study groups, PPI and placebo, were pooled and compared.

All authors had access to the study data and reviewed and approved the final manuscript.

Side Effects

No serious side effects in the intervention or placebo group were registered. One patient experienced diarrhea for 3 days, occurring after 1 month of treatment, which turned out to be a Campylobacter infection. The same patient described more fatigue at the end of the study. After deblinding, this patient was in the PPI group and needed 3 phlebotomies in total. Two patients described an unpleasant feeling in the stomach. One patient, taking placebo, was also more fatigued after 12 months' study time and 3 phlebotomies. Increasing arthralgia was described in 3 patients (2 placebo, 1 PPI group).

One patient withdrew after 10 months because of fatigue (PPI group), 1 patient had transient increased liver tests during an episode of viral upper airway infection (placebo group) and 1 patient had increased liver tests suggested to be steatohepatitis and confirmed by sonography (PPI group). The magnesium and vitamin B12 concentrations remained in the normal range in all patients.

Supplementary Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Homozygous p. C282Y mutation	Chelating therapy
Maintenance therapy for at least 12 months	Forced dietary regimen
$\geq$ three phlebotomies/year	Mentally incapable
SF level: 50-100 μg/L	Women being pregnant or planning to become pregnant
Age: 18-75 years	Patients with malignancy
Weight: $>$ 50 kg	BMI: $\geq$ 35kg/m^2
	On PPI treatment or earlier side effects

SF, Serum ferritin; BMI, Body Mass Index; PPI, Proton Pump Inhibitor.