Proton Pump Inhibitors Reduce the Frequency of Phlebotomy in Patients With Hereditary Hemochromatosis

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Q5 **BACKGROUND & AIMS:** **Patients with hereditary hemochromatosis (HH) need frequent phlebotomies to reduce iron overload. Proton pump inhibitors (PPIs) were reported to reduce the need for phlebotomies in patients homozygous for the C282Y mutation in *HFE*. We investigated the effects of PPI treatment on numbers of phlebotomies in these patients.**

METHODS: **We conducted a retrospective study of patients with HH homozygous for the C282Y mutation by using the database and medical records from Atrium Medical Centrum Parkstad in Brunssum, The Netherlands. In a paired group analysis of 12 patients, we compared mean serum levels of ferritin and number of phlebotomies needed each year during the periods of 3 years before and 3 years after the start of PPI therapy. We compared these results with those from a group who received PPIs for at least 2 years (n = 9) and a group who never received PPIs (n = 36).**

RESULTS: **We found a significant reduction in median number of phlebotomies after patients began taking PPIs vs before (0.50 vs 3.17, $P < .002$). Patients who received PPIs for at least 2 years needed significantly fewer phlebotomies than patients in the paired group before they started taking PPIs (1.25 vs 3.17, $P < .001$). The number of phlebotomies in the group who never received PPIs was significantly higher than in the paired group after they started taking PPIs (3.0 vs 0.5, $P < .001$).**

CONCLUSIONS: **On the basis of a retrospective analysis, in patients with HH homozygous for the C282Y mutation in *HFE*, treatment with PPIs for 2 or more years significantly reduced the number of phlebotomies required to maintain serum levels of ferritin below 100 μg/L.**

Keywords: Hepcidin; Dietary Iron Absorption; Heme; Phlebotomies; Genetic.

Hereditary hemochromatosis (HH) is one of the most common autosomal recessive genetic diseases. The average prevalence for the most frequent HFE gene polymorphism, C282Y homozygosity, is 0.41% in different white populations. In a meta-analysis, the average penetrance for clinical HH was 13.5% (1%–70%). A penetrance of 10% is accounted for in The Netherlands, leading to approximately 7000 patients.[1] HH is characterized by increased iron absorption from the gut. Hepcidin appears to be the most important regulating peptide for iron homeostasis, in which low levels of hepcidin lead to increased iron absorption.[2,3]

Increased dietary iron absorption can cause accumulation in parenchymal tissues, leading to severe organ damage in the heart, liver, joints, and endocrine organs. Without therapeutic interventions the excess of iron can cause cardiomyopathy, liver cirrhosis, arthropathy, diabetes, hypogonadism, and skin pigmentation.[4,5] To date, phlebotomy is still the standard therapy in which excess of iron is reduced by removing erythrocytes.[5,6] Guidelines of European Association for the Study of the Liver and American Association for the Study of Liver Diseases advise to decrease the serum ferritin (SF) levels less than 50 μg/L and to keep the SF levels at 50–100 μg/L in the maintenance period.[1,7]

Although phlebotomy is a very successful way to decrease iron overload, the procedure is accompanied with side effects and discomfort. Brissot et al[5] showed that in the induction phase, 52% of the patients experienced fatigue, fainting, and loss of appetite, and in the maintenance phase, 37% experienced these complaints.

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

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Overall, 16% would decide to quit with this therapeutic intervention when an alternative to decrease iron levels would be available. Other side effects after whole-blood donation are bruises (23%), sore arm (10%), and vasovagal reactions (7%).[8] The side effects of phlebotomy and the burden of treatment by loss of productivity and frequent hospital visits for bloodletting warrant investigation of alternative or complementary, less aggressive, and noninvasive therapies in the maintenance phase to reduce the number of phlebotomies. In the induction phase, however, phlebotomy and erythrocytapheresis are still the most effective treatments to reduce the iron overload.[9]

Clinical observations in HH patients on maintenance phlebotomy treatment showed that those who took proton pump inhibitors (PPIs) during longer periods needed fewer phlebotomies to maintain their SF level at around 50 μg/L. The intriguing question of what is the mechanism of this reduction in the number of phlebotomies was addressed by Hutchinson et al.[10] First, they showed that with a postprandial iron absorption test, non-heme iron absorption was significantly reduced when taking PPIs. Second, an observational retrospective case study with 15 HH patients homozygous for C282Y was performed. In a paired analysis of 7 HH patients, they showed a significant decrease in total phlebotomy blood volume in patients who used PPI (0.5 L per year) versus patients not on PPI medication (2.5 L per year).

Although the results of the above-mentioned study were convincing, further evidence of efficacy and safety is needed before PPIs could be advised as a therapeutic option in the treatment of HH patients. Therefore, we reviewed our HH population in a retrospective study with the aim to confirm the hypothesis that chronic use of PPIs reduces the frequency of phlebotomies in the maintenance treatment phase.

Methods

Study Design

We conducted a retrospective cohort study. All patients with HH were reviewed by using the electronic database and medical records at Atrium Medical Centrum Parkstad in Brunssum, a secondary medical center located in the south of Limburg, The Netherlands. Only patients with C282Y homozygosity, which was determined by genetic testing, were included. In a paired group, patients were included when data were available for at least 2 years before and 2 years after the start of PPI treatment. In the unpaired PPI group, patients were included when they were on PPI treatment for at least 2 years, and inclusion in the paired group was not possible because they were already on PPI treatment when they were diagnosed. Patients with intermittent PPI use were excluded. In the unpaired-no PPI group, patients were included who were not on PPIs, and data were available for at least 2–3 years (Figure 1). During the recording period all patients were on maintenance phlebotomy therapy.

Phlebotomies were carried out according to the European Association for the Study of the Liver guidelines when SF was greater than 100 μg/L unless valid reasons led to watchful waiting. Per single treatment procedure, 500 mL whole blood (equals 200–250 mL red blood cells) was withdrawn after puncturing a superficial vein of the forearm with a 16-gauge (1.6-mm) straight needle by using a mixing device and a collection bag (Compo Guard and Compo Select T 3941, respectively; Fresenius SE, Bad Homburg, Germany). SF levels were determined every 3 months. Patients gave informed consent for using their medical information.

Patients

From a total of 120 HH patients with genetically proven C282Y homozygosity, 57 patients were eligible for 1 of the 3 groups. The remaining patients could not be included because of reasons shown in Figure 1. In a paired design, we included 12 patients (7 male, 5 female) to compare the frequency of phlebotomies during a period of 3 years before start of PPIs with a period of 2–3 years after the start of PPIs. In addition, an unpaired PPI group was conducted with 9 patients (7 male, 2 female) who were on long-term PPI treatment for various reasons (Table 1). In the unpaired-no PPI group, 36 patients (23 male, 13 female) were included who were not on PPI treatment. The mean age at the time of analysis in the paired group was 69.9 years (standard error, 5.160) and was significantly higher when compared with 64.8 years (standard error, 5.142) in the unpaired PPI group ($P = .049$) and 59.53 years (standard error, 9.626) in the unpaired-no PPI group ($P = .001$).

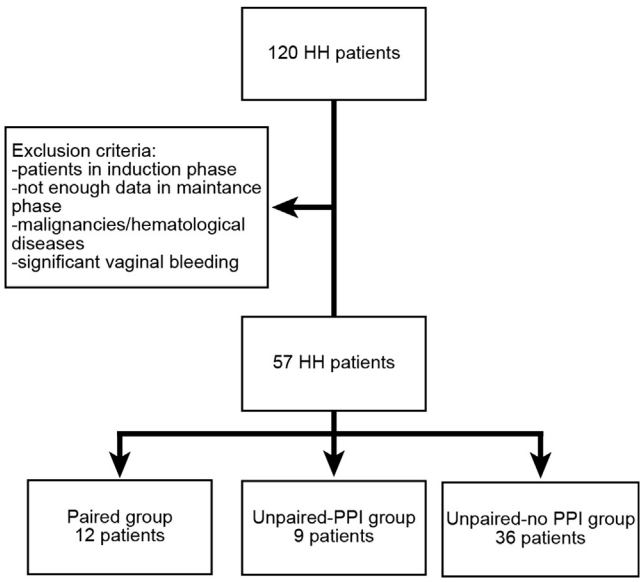

Figure 1. Flow chart of study design.