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Efficacy and Safety of Erythrocytapheresis and Low-Dose Erythropoietin for Treatment of Hemochromatosis

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BackgroundThe aim of this study was to determine retrospectively the efficacy of combined therapy using erythropoietin (EPO) and erythrocytapheresis (EA) in patients with hereditary hemochromatosis (HH) who did not tolerate phlebotomy.

Patients and Methods Twenty patients (age range, 43–74 years) with genetically confirmed HH had received low-dose EPO (4,000 IU) in accordance to the patient's hemoglobin levels between each EA session. Laboratory parameters including hemoglobin, ferritin, transferrin, and iron were measured at regular intervals.

ResultsAnemia did not occur in a single patient and no serious side effects were observed. Combined treatment with EPO and EA was well tolerated, and all 18 patients who suffered from fatigue prior to therapy recovered. Median ferritin values were 678.5 ng/L before treatment and 145 ng/L after treatment.

ConclusionEA in combination with EPO is safe and effective in treating patients with HH. Prospective studies comparing this therapeutic option to phlebotomy are warranted. J. Clin. Apheresis 00:000–000, 2016.

Key words: hemochromatosis; erythropoietin; erythrocytapheresis; phlebotomy; biosimilar

INTRODUCTION

Hemochromatosis (HH) is a disorder of iron metabolism with an overload of iron in the body due to an increase in intestinal absorption. Without adequate treatment, the increased iron deposition in tissues leads to progressive organ damage [1,2]. Phlebotomy is the standard treatment for HH. A standard session involves the removal of 500 mL of whole blood in 15–30 min. If treatment is well tolerated, therapeutic phlebotomy is performed once or twice weekly until ferritin levels decline to <50 μg/dL and transferrin saturation below 30–50% [3–6]. However, the hemoglobin concentration should not fall below 11 g/dL. In such cases, the interval of treatment is extended to every 3 weeks [7]. Therapeutic phlebotomy is a relatively safe and effective inexpensive form of treatment, but may cause temporary hypotension, bruising and injury of blood vessel walls, exhaustion and fatigue, loss of plasma proteins and leukocytes, and susceptibility to infection [4,8]. Fatigue and joint pain have been reported in 60% and 50% of patients with HH, respectively [9]. Other forms of therapy include dietary changes, the use of chelating agents such as desferal, ferriprox, and exjade, and erythrocytapheresis (EA), which involves the rapid removal of iron [6,7,10,11]. EA removes large amounts of red blood cells (RBCs) within a short period of time, making it beneficial for patients with severe iron overload or with intolerance to phlebotomy [6]. However, both treatment options are limited by the development of anemia. The initial use of EA was first described in 1983 in three patients with HH [12] and later confirmed in several studies [7,13–18]. Intensification of therapy [19] by isovolemic EA (1,000 mL every 4 weeks) was not superior compared with phlebotomy [19,20]. Anemia or developing anemia remains rather limited for all of the aforementioned therapeutic options. EA has been shown to be better tolerated by patients and its effects are faster and more effective than for phlebotomy [4,7,21,22]. The rapid depletion of iron stores is of importance for the patient, both physiologically and psychologically.

The aim of this study was to evaluate the efficacy and safety of combination therapy with EPO and EA in HH patients; who did not tolerate standard phlebotomy.

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TABLE I. Haematological and Iron Parameters Prior To and Following Combined Therapy

ID	Nr. of EA	Total amount of RCC (mL) removed	Nr of EPO injections	Hb (g/dL) pre/post therapy (difference)	Ferritin (μg/L) pre/post therapy (difference)	Iron (μg/dL) pre/post therapy (difference)
1	2	1,000	7	14.1/12.2 (−1.9)	152/48 (−104)	107/46 (−61)
2	4	2,000	18	12.4/12.8 (+0.4)	174/39 (−135)	125/95 (−30)
3	2	800	2	13.4/13.8 (+0.4)	214/73 (−141)	175/184 (+9)
4	7	3,500	9	15.6/16.1 (+0.5)	263/85 (−178)	147/189 (+42)
5	3	1500	9	14.7/15.0 (+0.3)	324/112 (−212)	216/131 (−85)
6	2	800	9	14.4/13.9 (−0.5)	329/172 (−157)	139/177 (+38)
7	4	2,000	12	14.0/15.1 (+1.1)	508/151 (−357)	248/137 (−111)
8	3	1,200	9	15.6/15.5 (−0.1)	537/264 (−273)	244/156 (−88)
9	4	1,600	9	14.4/13.4 (−1.0)	585/21 (−564)	171/61 (−110)
10	3	1,500	14	14.8/14.0 (−0.8)	664/165 (−499)	149/66 (−83)
11	9	4,500	16	15.5/16.0 (+0.5)	693/37 (−656)	223/99 (−124)
12	4	2,000	9	14.2/14.3 (+0.1)	946/191 (−755)	230/150 (−80)
13	11	5,500	30	14.6/16.6 (+2.0)	996/244 (−752)	248/191 (−57)
14	13	5,200	15	15.6/13.8 (−1.8)	1,100/669 (−431)	199/186 (−13)
15	4	2,000	16	14.5/16.1 (+1.6)	1,286/39 (−1,247)	113/79 (−34)
16	16	8,000	57	14.2/14.2 (0)	1,346/168 (−1,178)	270/148 (−122)
17	8	4,000	19	15.2/15.6 (+0.4)	1,363/139 (−1,224)	124/49 (−75)
18	14	5,600	62	14.1/15.8 (+1.7)	1,397/597 (−800)	220/227 (+7)
19	11	5,500	21	14.5/16.2 (+1.7)	2,043/179 (−1,864)	223/94 (−129)
20	38	15,200	207	12.9/14.1 (+1.2)	2,563/41 (−2,522)	192/143 (−49)

EA, erythrocytapheresis; EPO, erythropoietin; Hb, haemoglobin; ID, patient identification number; Nr, Number; and RCC, red cell concentrate.

MATERIALS AND METHODS

Study Population and Design

Between April 2006 and December 2012, 20 patients (18 males, 2 females) with symptomatic HH and elevated ferritin levels were treated with both EA and EPO. Combination therapy was performed only when treatment with phlebotomy was not possible or not desired by the affected patient. The patients had a median age of 48.5 years. Diagnosis was previously known for 14 patients and 6 patients were newly diagnosed (Table I). Thirteen patients had previously undergone treatment with phlebotomy and one patient had undergone combination therapy with phlebotomy and deferasirox (Exjade).

HH was confirmed by genetic testing in a reference laboratory, revealing 12 patients to be C282Y homozygote, 6 patients C282Y heterozygote, 1 patient H63D homozygote, and 1 patient C282Y + H63D heterozygote. An ethics vote was not necessary according to the Ethics Committee, since the study was a retrospective analysis of data from a private practice in Munich that remained anonymized. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Combination Therapy

EA was performed every 2 weeks using the Mobile Collection System MCS3P (Haemonetics, Braintree, MA). At each session, 500 mL of packed red blood cells were removed. Between each EA session, the patient was subcutaneously administered 4,000 IU EPO (Janssen-Cilag GmbH, Neuss, Germany). Between two sessions, the patient received between 1 and 6 injections of 4,000 IU EPO that was determined in accordance to the hemoglobin concentration of each individual patient. The maximum targeted hemoglobin concentration for males was 17 g/dL and for females 16 g/dL. Combination therapy was stopped when the ferritin concentration reached normal levels (males, 20–250 μg/L; females, 10–150 μg/L) or below 50 g/L, or when symptoms resolved.

Statistics

Unless indicated, values are represented as median and range. Normal distribution of the different parameters between the groups was analyzed using the Kolmogorov–Smirnov test. The paired *t* test or the Wilcoxon matched-pairs rank test was applied to determine normal distribution. *P* values less than 0.05 were considered as significant. Statistical analysis was performed using Graph Pad Prism version 6 for Windows (La Jolla, CA).

RESULTS

Haematological Parameters

Approximately 800–15,200 mL of packed cells were removed from each patient (Table I). No significant changes were observed in the hemoglobin

concentration and platelet numbers ($P = 0.2544$ and $P = 0.8041$, respectively) following therapy (Table I). In one patient, the Hb concentration was observed to decrease by 1.9 g/dL following therapy (Patient 1), whereas Hb was observed to increase by 2 g/dL in Patient 13. Symptoms of anemia were not observed in a single patient during the course of treatment. There was no increase in platelet numbers post-therapy as a result of EPO administration. In two patients, platelet numbers were increased by over $50 \times 10^{3}/\mu L$ (Patients 1 and 17), whereas a reduction of over $50 \times 10^{3}/\mu L$ was observed in a further two patients (Patients 12 and 19).

There was no significant change in mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) prior to and post therapy ($P = 0.2655$ and $P = 0.4171$, respectively). The MCV (normal value, 80–96 fL) was slightly or moderately increased in 10 patients before and after therapy. The MCH (normal value, 28–32 pg) was found to be slightly or moderately increased in 15 patients before therapy and 10 patients following therapy, although these changes were not significant.

Iron and Transferrin Levels Before and After EPO Therapy

Ferritin levels were reduced to within normal ranges in all patients (Table I). The median ferritin value was 678.5 ng/L (range, 152–2563 ng/L) before treatment and significantly decreased to a median value of 145 ng/L (range, 21–669 ng/L) after treatment ($P < 0.0001$). In two patients with high final ferritin concentrations, no further EA could be performed (Patients 13 and 14) due to lengthy travel times. The median ferritin difference, calculated as the difference between the baseline and final value, was found to be 531.5 ng/L (range, 104–2,522 ng/L).

The median concentration of transferrin significantly increased from 208 mg/dL prior to EPO and EA therapy to 237.5 mg/dL ($P = 0.0001$) following therapy. Iron was observed to decrease from a median 195.5 μg/dL before therapy to 140 μg/dL ($P = 0.0001$) following combined EPO and EA therapy.

Side Effects and Tolerance to Therapy

Symptoms of iron overload resolved. Therapy was well tolerated by all patients with a compliance of 100%. A mild citrate reaction was observed in two patients. Another patient was found to suffer from pleurisy as a result of an infection, although this was most likely not associated with treatment. No other side effects, including anemia, were observed or reported by the patients.

Cost of EPO Therapy

The price at the time of the study was approximately 80 € per injection. The mean cost was found to be 480.82 € (range, 66.32–6,864.12 €) per patient.

DISCUSSION

To avoid anemia within the course of EA therapy, EPO may present an alternative option. Recombinant EPO preparations have been successfully used in the treatment of, and/or to prevent, the development of anemia, even in preterm infants [23–25]. Treatment with EPO is also a long-term option, for example in dialysis patients, and is relatively low-risk and has become rather inexpensive due to the availability of "biosimilar" [26]. Via the availability of biosimilar, EPO prices have plummeted and the costs in the overall therapy are most likely, at present, significantly reduced. Furthermore, iron, which is present in excess amounts in HH, increases the effectiveness of EPO. Thus, EA in combination with EPO administration is an attractive alternative therapy for patients with HH.

A limited number of studies have addressed the use of combination therapy using EPO and EA in HH patients. In one study, each patient ($n = 10$) was administered 4,000 IU of EPO three times per week and ferritin levels were successfully reduced to normal following 3.25 months of therapy [27]. In the study by Mercuriali et al., patients ($n = 6$) received subcutaneous 40,000 IU EPO per week and EA was performed approximately every 2 weeks [28]. In these cases, target ferritin levels were achieved following an average 2.75 months. No side effects or development of anemia was observed, and the average hemoglobin at the end of therapy was 12.7 ± 0.8 g/dL. Furthermore, several case reports have been described of the successful treatment of patients with secondary HH using phlebotomy and EPO [29,30].

In our study, 20 patients with HH were treated using a combined therapy of EPO and EA. No side effects were observed and the presence of any symptoms, with the exception of joint pain in several patients, quickly receded. Hemoglobin concentrations were found to be primarily with the normal range during the entire period of treatment. Therefore, the administration of EPO not only prevented the development of anemia, but possibly an additional enhanced iron resorption in the intestine.

The overabundance of iron may also explain the increased values of MCV and MCH in the patients in this study. Both MCV and MCH values were elevated prior to the commencement of treatment in all patients and remained increased. It is believed that the increase in MCV and MCH values may be caused by an increased incorporation of iron into hemoglobin molecules [31–33]. This phenomenon cannot be explained

solely by an increased supply of iron, because even after normalization of ferritin, both values remain elevated.

The reason behind why the iron and ferritin reduction in the treated patients was not significantly high may be explained by two reasons. First, the patients in this study represent a heterogeneous group. The vast majority of patients had been previously treated prior to inclusion in this study and ferritin levels strongly differed between the patients. Therefore, the concentration of EPO administered varied. Second, in order to achieve a significant reduction in ferritin, the dosage was rather low in the majority of patients. In a previous study, patients were administered 2 × 600 U/kg of body weight of EPO compared with a maximum of 300 U/kg of body weight in this study [34]. This is of great importance as the adjustment of the dose of EPO was individualized and based on the hemoglobin concentration of each patient.

Although the individual cost of treatment with EA or EPO is higher than in phlebotomy, on an overall scale, a reduction in the cost of therapy can be achieved or, at least, maintained. In addition, the costs may also be greatly reduced by the use of biosimilar, and the number of absent days from work is reduced as patients have longer therapy-free intervals.

Furthermore, no side effects such as fatigue, exhaustion, or shortness of breath were found in association with the reduction in hemoglobin. The hemoglobin concentration remained stable and no anemia developed in any of the patients in this study. On the contrary, hemoglobin levels were observed to increase in a number of patients that resulted in the patients under combined therapy with EPO and EA feeling more productive and agile. Through regular and close monitoring of hemoglobin concentrations, the combination therapy of EPO and EA is a safe procedure. Throughout therapy, the hemoglobin concentration remained within the normal range and the quality of life was found to increase significantly.

There were several limitations to this study. First, this study comprised of a small cohort of patients. Second, this is a retrospective, heterogeneous study. Patients were included that were previously under therapy. Third, there are several side effects that have been reported to be associated with the use of erythrocyte stimulating agents such as EPO. These include hypertensive encephalopathy and seizures, and potential but unconfirmed risks include tumor growth and progression [35–37]. Further studies should include a comparison of combined EA and EPO therapy versus combined phlebotomy and EPO treatment.

In conclusion, EA and EPO are a sensible alternative to conventional phlebotomy in patients with HH. This combined therapy is gentle, effective, and free of severe side effects. Furthermore, combined therapy may reduce the overall cost of treatment and number of absent days lost due to illness. We believe that at present, EA in combination with EPO is a modern and contemporary alternative to phlebotomy, providing steady hemoglobin levels.

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