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Combination treatment with an erythropoiesis-stimulating agent and intravenous iron alleviates anaemia in patients with hereditary haemorrhagic telangiectasia

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Abstract

Background. Patients with hereditary haemorrhagic telangiectasia (HHT) suffer from recurrent epistaxis and bleeding from gastrointestinal telangiectasias that occur despite otherwise normal haemostasis and result in iron deficiency anaemia with increasing severity. In advanced disease, anaemia may be severe, be irresponsive to iron supplementation, and may lead to red blood cell transfusion dependency.
Methods. We conducted a retrospective study at our Centre for Osler's Disease to evaluate the effectiveness of adding an erythropoiesis-stimulating agent (ESA) to intravenous iron supplementation in the management of anaemic HHT patients. Blood values and treatment parameters were collected for nine months before combination therapy (iron supplementation only) and 12 months during combination therapy (iron supplementation plus ESA).
Results. Four patients received intravenous iron and an ESA with mean weekly doses of 126 mg and 17,300 units (U), respectively. Mean haemoglobin improved significantly during combination therapy, from 106 g/L to 119 g/L ($p < 0.001$).
Conclusion. Anaemia can be alleviated in patients with HHT who are irresponsive to intravenous iron supplementation, by addition of an ESA. The proposed mechanism behind the iron irresponsiveness is that the anaemia is caused by a combination of recurrent haemorrhage and anaemia of chronic disease.

Key words: *Anaemia, erythropoiesis-stimulating agents, hereditary haemorrhagic telangiectasia, iron*

Introduction

Hereditary haemorrhagic telangiectasia (HHT) or Osler–Weber–Rendu syndrome is a rare autosomal dominant genetic disorder with varying degree of penetrance that results in abnormal vascular structures in different body organs (1,2). Major clinical manifestations include variable degrees of recurrent bleeding from mucosal telangiectasias and arteriovenous malformations together with neurological, pulmonary, hepatic, and cardiac complications caused by angiodysplasia and arteriovenous fistula formations (3). Diagnosis is based on the presence of at least three of the following characteristics: recurrent epistaxis, mucocutaneous telangiectasias, evidence of autosomal

dominant inheritance, and visceral arteriovenous malformations (AVMs) (1,4). The HHT diagnosis is classified as definite if three criteria are present, suspected if two criteria are present, and unlikely if fewer than two criteria are present (1,4). Chronic recurrent epistaxis and bleeding from gastrointestinal telangiectasias (most commonly gastric and duodenal) occur despite otherwise normal haemostasis and normal platelet function and result in iron deficiency anaemia of increasing severity. This manifestation is associated with deteriorated quality of life (5,6). Medical and surgical efforts to manage the vascular sources of bleeding in these patients are not always successful and are often short-acting. Accordingly, a substantial proportion of middle-aged and elderly HHT patients

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suffer from chronic iron deficiency anaemia and become dependent on red blood cell (RBC) transfusions. Treatment of anaemia in these patients is not evidence-based due to the absence of clinical trials addressing this issue. Routine supportive therapy for these patients includes regular RBC transfusions and iron supplementation. The role of erythropoiesis-stimulating agents (ESAs) with or without iron supplementation in the management of renal anaemia (7,8), anaemia of chronic disease (9-12), cancer (13,14), and chemotherapy (15) has been well studied. However, the effect of use of ESAs in combination with intravenous (i.v.) iron supplementation in the management of chronic anaemia in HHT patients is not known. In Uppsala University Hospital, patients with HHT are treated by a multidisciplinary group of experts (Uppsala University Hospital's Centre for Osler's Disease). Patients with severe iron deficiency anaemia requiring i.v. iron supplementation and/or RBC transfusions are referred to the haematology day care for anaemia treatment and follow-up. Since HHT is an orphan disease, a trial design other than a controlled trial may thus be considered of value. In this retrospective study we evaluated if anaemic HHT patients not responding to i.v. iron supplementation responded to combination treatment with iron supplementation and an ESA.

Material and methods

During 2012–2013, we identified all HHT patients suffering from chronic anaemia requiring active treatment via our haematology department. We specifically studied patients with anaemia that had not been alleviated by i.v. iron supplementation. Treatment with an ESA was added to the iron supplementation in these patients in an attempt to increase their haemoglobin (Hb) values. Since this treatment was outside the clinical trial setting, dosing of ESA and iron was individualized for each patient. The aim of this retrospective study was to evaluate if HHT patients with chronic anaemia not responding to i.v. iron supplementation respond to combination treatment with an ESA and i.v. iron supplementation with a Hb increase. The case records of the patients were reviewed and the mean values for Hb, mean corpuscular volume (MCV), and ferritin were compared before (i.v. iron) and during combination treatment (iron plus ESA). Furthermore, the mean weekly doses of iron and ESA and the number of units of packed RBC transfused were compared before and during combination treatment. At our laboratory, reference values for Hb are 130–170 g/L and 120–150 g/L for men and women, respectively. For MCV, the reference range is 82–98 femtolitre (fL), and for ferritin the reference ranges are 25–310 µg (microgram)/L and 10–155 µg/L for men and women, respectively. Data were collected for an average of 9 (range 8–12) months during i.v. iron supplementation and for 12 months during combination treatment.

This study was approved by the Regulatory Ethics Committee of Uppsala and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Statistical analyses were performed using the SigmaPlot 11 software package (Systat Software, San Jose, CA, USA). Quantitative variables were expressed as means ± standard deviations. The Student's *t* test or Mann–Whitney rank sum test was used to compare variables. A *p* value of less than 0.05 was considered statistically significant.

Results

At our Centre for Osler's Disease, we identified nine patients with severe chronic anaemia who were being treated with i.v. iron supplementation with or without regular RBC transfusions. Four of these patients had severe anaemia not alleviated by i.v. iron supplementation. Patient characteristics for these patients are presented in Table I. None of the patients suffered from B12 or folate deficiency, hypothyroidism, haemolytic anaemia, chronic renal failure, or any haematologic malignancy that could contribute to their anaemia. Patients number 1 and 2 suffered mainly from haemorrhage from telangiectasias in the gut, whereas the major cause of blood loss for patients 3 and 4 was epistaxis. Two of the patients received iron sucrose and low-molecular-weight iron dextran as iron supplementation, whereas the other two patients received iron sucrose and iron polymaltose, respectively. The type of ESA administered was epoetin alfa and epoetin beta (two patients for each type). Mean Hb for these patients did not change before and after initiation of i.v. iron supplementation (data not shown), whereas mean Hb increased

Table I. Patient characteristics of the four anaemic Osler's disease patients irresponsive to intravenous iron supplementation.

Patient no.	Age (y)	Sex (F/M)	Age at diagnosis (y)	Osler diagnosis (definite/suspected/ unlikely)
1	63	M	54	Suspected
2	63	F	51	Suspected
3	69	F	39	Definite
4	63	F	51	Definite

F = female; M = male.

Table II. Laboratory data for the patients during intravenous iron supplementation (prior to combination treatment) and during combination treatment (erythropoiesis-stimulating agent plus intravenous iron). Data are expressed as mean ± SD.

Parameter	Prior to combination treatment	During combination treatment
Hb (g/L)	106 ± 9	119 ± 19[a]
MCV (fL)	85.7 ± 4.6	82.9 ± 5.3
Ferritin (µg/L)	67 ± 30	68 ± 58

[a]$p < 0.001$.
Hb = haemoglobin; MCV = mean corpuscular volume; fL = femtolitre.

significantly from 106 g/L to 119 g/L when an ESA was added to i.v. iron (Table II). The increase in mean Hb observed after addition of an ESA to i.v. iron was not associated with any change in mean ferritin, and mean MCV was within the reference range before and during combination treatment (Table II). The mean weekly dose of i.v. iron administrated during iron supplementation alone and during combination treatment was 125 mg and 126 mg, respectively. The mean weekly dose of ESA was 17,300 U (Table III), but the dose required to achieve an increase in Hb varied considerably between the individual patients (data not shown). The Hb increase observed during combination treatment did not decrease the patient's need for RBC transfusions (Table III).

Discussion

In this retrospective study, we report, for the first time, good effectiveness when combining i.v. iron supplementation with an ESA in the treatment of HHT patients with chronic anaemia.

Table III. Dosing of intravenous iron and erythropoiesis-stimulating agent during iron supplementation and during combination treatment (erythropoiesis-stimulating agent plus intravenous iron). Data are expressed as mean ± SD.

Parameter	Prior to combination treatment	During combination treatment
Dose of i.v. iron (mg/week)	125 ± 40	126 ± 68
Dose of ESA (U/week)	0	17,300 ± 15,300
Number of RBC units transfused (units/month)	0.23 ± 0.28	0.44 ± 0.56

ESA = erythropoiesis-stimulating agent; RBC = red blood cell; U = unit.

Four of our HHT patients with recurrent gastro-intestinal haemorrhage and/or epistaxis had anaemia that was not alleviated during i.v. iron supplementation. Anaemia in HHT is commonly attributed to absolute iron deficiency caused by chronic haemorrhage (1,3). The lower reference limits for ferritin in our laboratory are 10 µg/L and 25 µg/L for women and men, respectively. However, using ferritin 30–50 µg/L as the cut-off for absolute iron deficiency in elderly patients with concomitant diseases increases the sensitivity considerably (16-19). Even if a ferritin cut-off of 50 µg/L is used for the diagnosis of absolute iron deficiency in this group of patients, it is less likely that the lack of effect of iron supplementation observed is solely caused by iron-restricted erythropoiesis, since the mean ferritin was 67 µg/L and mean MCV was not subnormal. In addition, Hb increased significantly after addition of an ESA without any increase in the mean weekly dose of iron administered or increase in mean ferritin. Our hypothesis on the lack of response to i.v. iron in these patients is that their anaemia is caused by a combination of recurrent haemorrhage and anaemia of chronic disease (20), since all four patients suffered from concomitant illnesses. Two of the patients were diagnosed with congestive heart failure (CHF) secondary to high-output heart failure associated with HHT (21,22), and the other two with chronic arthritis and chronic obstructive pulmonary disease (COPD) with frequent exacerbations, respectively. Anaemia is common in CHF and chronic arthritis, and responds well to ESA treatment (9-12,23). It is conceivable that the infectious exacerbations in the patient with COPD induced anaemia of chronic disease. However, we could not properly assess the degree of inflammation biochemically in the patients since C-reactive protein and erythrocyte sedimentation rate were not analysed, or were analysed on only a few occasions during the observation period. No decreased need for RBC transfusions was observed during combination treatment. The reason for this is probably that patients with advanced HHT usually develop short episodes of acute haemorrhage with severe anaemia requiring multiple blood transfusions. Combination therapy with i.v. iron and ESA may have an anti-anaemic effect in HHT. However, data presented here should be interpreted with some caution since they are obtained relative to baseline measurements in a case series. As only four patients were included no firm conclusions on drug safety may be drawn other than on acute serious adverse events (SAE); however, no such acute SAEs were observed.

In summary, anaemia can be alleviated in patients with HHT who are irresponsive to i.v. iron supplementation, by addition of an ESA. The proposed

mechanism behind the iron irresponsiveness is that the anaemia is caused by a combination of recurrent haemorrhage and anaemia of chronic disease.

Acknowledgements

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