TRANSFUSION MEDICINE AND TRANSFUSION COMPLICATIONS

Original article

Intravenous ferric carboxymaltose is effective and safe in patients with inflammatory rheumatic diseases

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Background - The aim of this study was to evaluate the efficacy and safety of ferric carboxymaltose in rheumatic patients with iron deficiency anaemia.

Materials and methods - The study retrospectively evaluated a cohort of 34 patients with iron deficiency anaemia affected by inflammatory rheumatic diseases that are refractory or intolerant to oral iron therapy. They were treated with ferric carboxymaltose for a total of 56 cycles of treatment. The primary end point was to evaluate the increase of haemoglobin after ferric carboxymaltose treatment. The secondary end point was safety, including the occurrence of disease flare.

Results - Median age of the cohort was 60 years (range 31-91 years), with a male/female ratio of 4/30. Nine (26.5%) were affected by rheumatoid arthritis, 10 (29.4%) by spondyloarthritis, and 15 (44.1%) by other autoimmune connective tissue diseases. Median time from diagnosis was 7 years (IQR 2-12). At time of treatment (T_0), median haemoglobin was 9.3 g/dL (IQR 8.2-10.3), transferrin saturation 6.2% (IQR 3.8-9.8), and ferritin 8.5 ng/mL (IQR 6.0-12.8). Median ferric carboxymaltose dose was 1,000 mg. At 6 weeks from T_0, median haemoglobin was 12.3 g/dL (IQR 11.6-13.3), with a mean increase of 3.0 g/dL ($p<0.01$). Twelve (35.3%) patients needed re-treatment with ferric carboxymaltose for recurrence of iron deficiency anaemia. Four (4.3%) patients developed mild grade side effects. One suspected flare reaction has been observed.

Discussion - In patients affected by inflammatory rheumatic diseases, ferric carboxymaltose is safe and effective in correcting iron deficiency anaemia.

Keyword: *ferric compounds, anaemia, iron-deficiency, rheumatic diseases.*

INTRODUCTION

Iron deficiency (ID) affects more than 2 billion people worldwide[1], and ID anaemia (IDA) remains the main cause of anaemia, as confirmed by the analysis of a large number of reports on the burden of disease carried out in 187 countries between 1990 and 2010[2]. Anaemia is a frequent comorbidity in patients with systemic rheumatic diseases, and has a negative influence on the patient's quality of life, physical activity, and cardiovascular physiology[3-5]. The prevalence and aetiology of anaemia varies among different

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inflammatory rheumatic diseases, which is partly due to differences in the specific pathophysiology and treatment status, and other patient-related factors[6].

The relative or absolute ID is frequently observed in inflammatory rheumatic diseases. During inflammation, iron homeostasis and transcellular iron fluxes are substantially altered, leading to restricted availability of iron (relative deficiency) for erythropoiesis due to the action of hepcidin, a liver-derived peptide[7]. Patients with systemic inflammatory diseases can also frequently have absolute deficiency of iron. Autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) usually affect menstruating women. Furthermore, these diseases are often complicated by chronic gastrointestinal bleeding as a consequence of the underlying disease (e.g., inflammatory bowel disease), and treatments such as non-steroidal anti-inflammatory drugs (NSAID) and glucocorticoids[7-8]. Moreover, ID can result from impaired iron absorption due to autoimmune gastritis, coeliac disease or *Helicobacter pylori* infection, which can occur as a concomitant disease in patients with rheumatic disease[9].

Management of IDA involves treatment of the underlying cause to prevent further iron loss and iron supplementation, both to correct anaemia and to replenish body stores[10,11]. Oral iron is the simplest choice, but its use in a patient with inflammatory rheumatic disease is limited by side effects (diarrhoea or constipation, epigastric discomfort, nausea, and abdominal pain) and by reduced absorption (inflammation and drugs). For those intolerant or not responding to oral iron, the available parenteral preparations could be a valid option. All intravenous (i.v.) iron formulations have a small risk of causing allergic reactions, which can be life-threatening if not treated promptly. Practical recommendations for minimising this risk include a slow infusion rate, careful patient observation, and administration by trained health care personnel in an environment with access to resuscitation facilities[12]. Older intravenous preparations, such as total dose high-molecular-weight iron dextran (HMWID), have been associated with excessive iron in the synovium, resulting in joint damage, and with anaphylaxis and exacerbation of synovitis in patients affected by RA[13-15]. More recently, sodium ferric gluconate complex in sucrose injection and iron sucrose were administrated in RA patients with IDA and was observed to be safer than HMWID: no anaphylaxis was observed, while flare-up of disease was rare and mild[16,17]. Sodium ferric gluconate and iron sucrose are not very stable and thus contain a higher percentage of labile weakly-bound iron, requiring administration of repeated low doses of iron[11,18-19]. Ferric carboxymaltose (FCM) is a non-dextran preparation which can be administered at a single dose of up to 1,000 mg by i.v. infusion over at least 15 minutes[11,20-21]. The simple and fast administration, the single high dose, and its safety profile suggest FCM is an ideal i.v. iron formulation; however, there is no record about its use in patients with inflammatory rheumatic diseases.

In this study, we evaluated whether treatment with FCM is effective and safe in a retrospective cohort of patients with IDA affected by inflammatory rheumatic diseases.

MATERIALS AND METHODS

Patients

We retrospectively collected the data of patients with IDA affected by inflammatory rheumatic diseases who were treated with FCM from May 2015 to December 2017 in the Department of Immunohaematology and Transfusion Medicine of Bolzano Hospital. The diagnosis of inflammatory rheumatic diseases was made in the local Rheumatology Unit according to international criteria specific for each disease. We subdivided patients into three groups according to diagnosis: RA, spondyloarthritis (e.g. ankylosing spondylitis [AS], psoriatic arthritis [PsA] and enteropathic arthritis), and other autoimmune connective tissue diseases (CTD) (SLE, Sjögren syndrome [SS], systemic sclerosis [SSc]; mixed connective tissue disease [MCTD], or undifferentiated connective tissue disease [UCTD]). Iron deficiency was defined by ferritin <12 ng/mL or <100 ng/mL during inflammation or transferrin saturation (TSAT) <20%[22]. Routine haematological evaluation of a patient with IDA in our institute included a survey for disorders of gastrointestinal and gynaecological tract. Patients affected by active cancer were excluded. Informed consent was obtained from all patients included in the study. The study was approved by the local ethics committee.

Iron supplementation

The total dose of iron administered was calculated using the FCM product information dosing scheme, taking into account the patient's haemoglobin (Hb) concentration and body weight[23]. FCM (Ferinject®, Vifor, Saint Galene, Switzerland) was administered by i.v. infusion at doses

of 500-1,000 mg in 100-250 mL normal saline 0.9% over 15-20 minutes; the patients were monitored for 30 minutes after infusion. FCM was given weekly at a maximum dose of 1,000 mg/week. Contraindications to i.v. iron were active infection and hypersensitivity to i.v. iron formulations or any of their inactive components. Patients were scheduled for a follow-up visit 6 weeks after receiving the total dose of iron to check the haematological response. Rheumatological follow up was scheduled according to the rheumatological disease; clinical conditions of the patient, disease activity indices and medications were all carefully assessed by the rheumatologist at each visit. Re-treatment with FCM was started when IDA was noted during the follow up.

End points and their definition

The primary end point was to evaluate the increase of Hb from basal level 6 weeks after FCM treatment. The secondary end points were:

- rate of achievement of correction of anaemia (Hb level ≥12 g/dL in females or ≥13 g/dL in males);
- evaluate the increase in mean corpuscular volume (MCV), mean cell haemoglobin (MCH), and ferritin after 6 weeks of FCM treatment;
- evaluate the rate of side effects and disease flare after FCM treatment.

Statistical analysis

Demographic, clinical and laboratory characteristics of patients were analysed by descriptive statistics. Absolute and relative frequencies have been reported.

The statistical significance of differences in haemoglobin, red blood and iron indices observed at baseline (T_0) and at the follow-up visit (T_1) was determined by using the Wilcoxon test or paired *t*-test, according to the normality of variables. $p<0.05$ was considered statistically significant. All analyses were performed by using SPSS Version 18.0 (SPSS Statistics; IBM, Armonk, NY, USA).

RESULTS

Patients' characteristics

A total of 34 patients were evaluated; baseline characteristics of the study participants are detailed in **Table I**. At the time of the first FCM treatment, the median age of the cohort was 60 years (range 31-91 years), with a male/female ratio of 4/30. Nine (26.5%) were affected by RA, 10 (29.4%) by spondyloarthritis, and the other 15 (44.1%) by other autoimmune CTD. Median time from diagnosis was 7 years (IQR 2-12 years); in 2 patients, IDA was detected at the onset of the disease. As specific therapy, 23 (67.6%) took steroids, 22 (64.7%) disease-modifying anti-rheumatic drugs (DMARDs), and 5 (14.7%) biological drugs. Four (11.8%) patients were in remission and did not need immunosuppressive therapy. One or more concurrent causes of anaemia were detected in 16 (47.0%) patients. Four (11.8%) patients had needed transfusion support in the previous six months. Finally, 16 (47.1%) patients took antiplatelet or anticoagulant therapy and 22 (64.7%) proton-pump inhibitors.

Table I - *Patients' characteristics at baseline*

Variable	Patients (n)	Value
Sex, male (%)	34	4 (11.8%)
Age, years (range)	34	60 (31-91)
Diagnosis	34	
Rheumatoid arthritis		9 (26.5%)
Spondyloarthritis		10 (29.4%)
Autoimmune CTD		15 (44.1%)
Time from diagnosis, years (median, IQR)	34	7 (2-12)
Drugs	34	
None		4 (11.8%)
Steroids		23 (67.6%)
DMARDs		22 (64.7%)
Biological drugs		5 (14.7%)
Concurrent causes of anaemia	34	
Inflammation, CRP ≥0.5 mg/dL		6 (17.6%)
Chronic kidney disease, GFR <60 mL/min/1.73 m²		5 (14.7%)
Folate deficiency, <4.6 ng/mL		5 (14.7%)
Vitamin B12 deficiency, <191 pg/mL		3 (8.8%)
Autoimmune haemolytic anaemia		1 (2.9%)
Antiplatelet or anticoagulant therapy	34	16 (47.1%)
Patients transfused in the previous six months	34	4 (11.8%)
Indications to intravenous iron therapy	34	
Refractoriness to oral therapy		24 (70.6%)
Intolerance to oral therapy		2 (5.9%)
Haemoglobin ≤8 g/dL		8 (23.5%)

CTD: connective tissue diseases; CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs; GFR: glomerular filtration rate; IQR: interquartile range; FCM: ferric carboxymaltose.

Characteristics of ferric carboxymaltose treatment and its safety

The 34 patients received a total of 56 cycles of FCM treatment (**Table II**). Twelve (35.3%) patients received more than one cycle of treatment. At time of treatment (T_0), median (IQR) Hb was 9.3 g/dL (8.2-10.3 g/dL), TSAT 6.2% (3.8-9.8%), and ferritin 8.5 ng/mL (6.0-12.8 ng/mL). At T_0, a starting Hb value <10 g/dL was observed in 37 (66.1%) cycles of treatment. Median initial FCM dose was 1,000 mg (range 500-2,000 mg); a total dose equal to

Table II - *Characteristics of patients' and sessions for every treatment*

Variable	Treatment (n)	Value
Haemoglobin, g/dL (median, IQR)	56	9.3 (8.2-10.3)
TSAT, % (median, IQR)	40	6.2 (3.8-9.8)
Ferritin, ng/mL (median, IQR)	49	8.5 (6.0-12.8)
Weight, kg (median, IQR)	56	62.5 (56.0-67.5)
Cycle of treatments for patients	34	
1		22 (64.7%)
2		6 (17.6%)
3		4 (11.8%)
4		0 (0%)
5		2 (5.9%)
FCM dose, mg	56	
500		15 (26.8%)
1,000		27 (48.2%)
1,500		9 (16.1%)
2,000		5 (8.9%)
Number of infusions per cycle (total infusion: 94)	56	
1		27 (48.2%)
2		21 (37.5%)
3		7 (12.5%)
4		1 (1.8%)
Adverse drug reactions/infusion	94	4 (4.3%)
Flare of disease/cycle of treatment	56	1 (1.8%)

TSAT: transferrin saturation; CTD: connective tissue diseases; IQR: interquartile range; FCM: ferric carboxymaltose.

≥1,000 mg was administered in 41 (73.2%) cases. In 27 (48.2%) cycles of treatment, a single infusion was sufficient; the total number of infusions was 94. We observed 4 (4.3%) mild adverse drug reactions, 3 during infusion; one patient reported hot flushes, one nausea associated with abdominal pain, and the third urticaria. A further patient reported myalgia concurrent to mild hypophosphataemia two weeks after the treatment. Finally, the patient affected by urticaria developed a possible flare of the disease. She reported a recent diagnosis of SS associated with multiple autoimmune disorders (primary sclerosing cholangitis and polyglandular autoimmune syndrome type III), and was not under immunosuppressive therapy. She developed widespread arthralgia over the days following the treatment, which resolved spontaneously in a week.

Secondary end point: changes in haemoglobin and iron indices

After 6 weeks (T_1) from FCM treatment, the mean increase in Hb, MCV and MCH from baseline were respectively 3.0 g/dL, 9.8 ϕL and 3.9 pg (**Table III**); these increases between T_1 and T_0 were all statistically significant (p<0.01). The increase in Hb correlated with its T_0 value (p<0.01, R2 0.62). The mean increase in ferritin from baseline was 100 ng/mL. After 33 (58.9%) cycles of treatment, Hb values normalised. After only two cycles, we observed Hb <10 g/dL at T_1. In both cases, the T_1 value was increased in comparison to T_0. At T_1 an increase of ≥1 g/dL in Hb value was reported after 53 (94.6%) cycles of treatment, and of ≥2 g/dL after 38 (67.8%).

Table III - *Haemoglobin, red blood and iron indices before and after 6 weeks from ferric carboxymaltose (FCM) treatment*

Variable	Patients (n)	Baseline (T_0)	Follow-up visit (T_1)	p-value
Hb, g/dL (median, IQR)	56	9.3 (8.2-10.3)	12.3 (11.6-13.3)	<0.01
MCV, ϕL (median, IQR)	56	78.4 (73.1-85.6)	88.2 (81.9-92.4)	<0.01
MCH, pg (median, IQR)	56	24.0 (21.2-27.0)	27.9 (25.7-29.7)	<0.01
Ferritin, ng/mL (median, IQR)	35	8.5 (6.0-12.8)	109.0 (47.0-274.0)	<0.01

IQR: interquartile range; Hb: haemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin.

DISCUSSION

This study is, to the best of our knowledge, the first to investigate whether treatment with FCM is effective and safe in patients affected by inflammatory rheumatic diseases with IDA.

Results regarding effectiveness were as expected, showing a statistically significant increase in Hb, MCV, MCH and ferritin (p<0.01) after 6 weeks (T_1) from FCM treatment. In 33 (58.9%) cycles, Hb levels normalised. Many studies investigating FCM treatment in patients with IDA affected by different medical conditions (e.g., inflammatory bowel disease, heavy uterine bleeding) consider an increase of ≥2 g/dL in Hb value as indicative of a response to treatment[23-26]. At T_1, we observed a rate of increase of ≥2 g/dL in Hb in 67.8% of the treatment cycles, a result similar to that reported in literature[23-25].

The other great concern about the use of FCM in the setting of inflammatory rheumatic diseases is its safety. All intravenous iron formulations have a small risk of causing severe allergic reactions, and practice recommendations suggest administration by trained health care personnel in an environment with access to resuscitation facilities[12].

Early studies in humans suggested a negative impact of iron supplementation on disease activity among patients with RA receiving iron dextran infusions for anaemia[13-15]. One study demonstrated worsening of synovitis in all patients within 24-48 hours of such an infusion[14]. Nine of the 10 patients with RA who received iron dextran infusions had an exacerbation of arthralgia and joint dysfunction associated with an increase in erythrocyte sedimentation rate[13]. Whether these reactions represent a worsening of RA or simply a delayed hypersensitivity reaction is not clear. Regarding CTD, a case report describes the worsening of disease activity with an infusion of iron[27]. During our study, FCM was administered by a total of 94 infusions, and three mild adverse drug reactions were observed during the infusion: one patient reported hot flushes, one nausea associated with abdominal pain, and the third urticaria. These data are in accordance with the most recent publications, which reconsider the risk of allergic reaction and endorse the safety of all the current intravenous iron formulations[11,28]. Another patient reported myalgia concurrent to mild hypophosphataemia two weeks after the treatment. In literature, hypophosphataemia is reported after parenteral FCM injection and may have clinical consequences, including persistent fatigue[29]. Finally, the patient affected by urticaria developed a likely flare of the disease. She developed widespread arthralgia the days following the treatment, which resolved spontaneously in a week. She reported a recent diagnosis of SS associated with multiple autoimmune disorders (primary sclerosing cholangitis and polyglandular autoimmune syndrome type III), and was not on immunosuppressive therapy. Considering this report, it could be suggested that patients with an active autoimmune disease without adequate immunosuppressive therapy may be at greater risk of developing an allergic-type reaction or a disease flare.

Our study also emphasises additional issues about the epidemiology of IDA in inflammatory rheumatic diseases. Historically, anaemia is frequently observed in patients with chronic inflammatory diseases and is mainly an immune-driven disorder with alterations in iron homeostasis, impaired erythroid progenitor proliferation, and reduced biological activity of erythropoietin, along with a decrease in erythrocyte half-life at the centre of its pathophysiology[4]. In our cohort of patients with IDA, only 6 (17.6%) presented an increase in CRP value, suggesting a high prevalence of absolute ID. Regarding the prevalence of IDA in different inflammatory rheumatic diseases, Segal *et al.* reported that the incidence of low serum ferritin was significantly higher in SLE patients than in RA and spondyloarthritis groups (40% *vs* 11% and 14%, respectively)[6]. In our cohort, we also observed a higher prevalence of patients affected by autoimmune CTD (44.1%) with respect to RA (26.5%) or spondyloarthritis (29.4%). This different distribution may reflect a greater prevalence of absolute IDA compared to alterations of iron homeostasis due to inflammation in different diseases. As far as the aetiology of absolute IDA is concerned, inflammatory rheumatic diseases are often complicated by chronic blood loss (e.g., NSAID or glucocorticoids or anticoagulant therapy) or gastrointestinal malabsorption (e.g., proton-pump inhibitors therapy or associated autoimmune gastritis)[4,7,9]. At least a possible cause of chronic blood loss was present in 32 (94.1%) patients: a gynaecological cause in 12 (35.3%), while 23 (67.6%) patients took glucocorticoids, and 16 (47%) antiplatelet or anticoagulant drugs. Regarding possible malabsorption, 22 (64.7%) subjects took proton-pump inhibitors and 3 (7.9%) suffered from autoimmune atrophic gastritis. These results justify refractoriness to oral iron therapy, which was the indication of intravenous therapy in 26 (76.5%) patients. Finally, we observed one or more concurrent causes of anaemia in almost half of the patients, as reported in literature[6,30]. This observation confirms that anaemia in inflammatory rheumatic diseases is often multifactorial and a careful diagnostic workup is mandatory.

Our study presents some limitations. The most important of these is the limited and heterogeneous sample population; however, the previous studies in this setting also presented a limited sample size population[14-17]. Considering that 12 patients subsequently underwent further re-treatment (range 1-5), another possible major limitation of our study is the lack of a prospective evaluation of possible long-term side effects, especially for close monitoring of bone metabolism. Finally, we observed a discrepancy between effective and administered FCM dose. The total dose of sodium ferric gluconate and iron sucrose is traditionally calculated by the Ganzoni formula; however, the total dose of FCM was calculated taking into account the patient's Hb concentration and body weight[23]. For

example, a patient with Hb <10 g/dL weighing <70 kg should receive a FCM dose of 1,500 mg. In our study, the FCM total dose should have been based on the product information dosing scheme. However, we observed how often the administered dose was lower than expected (median 16 mg/kg). The correct dose was prescribed only in 14 cycles, while in 40 cases the effective administered dose was lower than that calculated. Considering an FCM dose as less or more than 16 mg/kg, at T_1 we observed an increase of >2 g/dL in Hb values respectively in 42.8% *vs* 85.7% of cases (p=0.01). The reduction in initial dose of FCM was likely to avoid additional patient hospital access or possible toxicity. However, this could reduce the efficacy of FCM treatment or require further re-treatment. Considering our effectiveness and safety results, we suggest a strict adherence to the recommended FMC dose.

CONCLUSIONS

In conclusion, to the best of our knowledge, these are the first data to support the effectiveness and safety of FCM in the management of IDA patients affected by inflammatory rheumatic diseases, especially in patients with a disease in remission or well controlled by immunosuppressive therapy.

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AUTHORSHIP CONTRIBUTIONS

US, FV and BR are responsible for the conception and design of the work. US, AA, AM, MD and BR managed the patients. US, BR and PCC collected data. FV performed statistical analysis. US, AA, PCP and BR wrote the manuscript. All Authors contributed to critical revision and final approval of the article.

The Authors declare no conflicts of interest.

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