



Improved Hemoglobin Response with Ferric Carboxymaltose in Patients with Gastrointestinal-Related Iron-Deficiency Anemia Versus Oral Iron

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Abstract

Aims To compare the efficacy and safety of intravenous (IV) ferric carboxymaltose (FCM) versus oral iron and other IV iron therapies in patients with iron-deficiency anemia (IDA) resulting from gastrointestinal (GI) disorders.

Methods A pooled analysis of four prospective, randomized, active-controlled trials in patients with IDA was performed. Efficacy measures included change from baseline in hemoglobin (Hb), ferritin, and transferrin saturation (TSAT) and correlations of baseline Hb, ferritin, and TSAT to change in Hb. The incidence and type of adverse events were evaluated.

Results A total of 191 patients were evaluated. The mean change in Hb from baseline to the maximum value was 0.8 g/dL with oral iron ($P=0.001$ vs. FCM), 2.2 g/dL with FCM, 2.0 g/dL with any IV iron ($P=0.391$ vs. FCM), and 1.9 g/dL with iron sucrose ($P=0.329$ vs. FCM). Patients treated with FCM and iron sucrose had larger increases in Hb. This effect may have been attributed to a lower baseline Hb level. Drug-related adverse events occurred in 11.9, 12, 26.2, and 25% and serious adverse events (SAEs) occurred in 6.9, 4, 9.8, and 12.5% of patients in the FCM, oral iron, other IV iron therapies, and iron sucrose groups, respectively. No SAEs were considered treatment related in the FCM group, compared with two treatment-related SAEs in two patients (6.3%) in the iron sucrose group.

Conclusions FCM is an effective therapy in patients with IDA who have GI disorders and has a safety profile comparable to that of other IV iron agents.

Keywords Hemoglobin · Inflammatory bowel disease · Ferric carboxymaltose · Iron

Introduction

In industrialized and developing countries, anemia is a common and widespread disorder. According to the World Health Organization, anemia affects approximately 25% of the global population (1.62 billion people) [1] and is

frequently caused by iron deficiency [2, 3]. Gastrointestinal (GI) diseases are a common cause of both iron deficiency and anemia. Patients with GI disorders such as inflammatory bowel disease (IBD) are at risk of development of iron-deficiency anemia (IDA) due to a combination of factors, including chronic blood loss, inflammatory-mediated impairment of intestinal iron absorption, and the inability to utilize existing iron stores [4–6]. The prevalence of IDA in IBD has been reported as high as 73.7% [7]. Similarly, celiac sprue is frequently complicated by the development of IDA, which can occur even in the absence of GI symptoms [8]. IDA without clinical evidence of intestinal malabsorption is encountered in approximately 50% of adults with subclinical celiac disease [9], while other studies have demonstrated that celiac disease is responsible for anemia in 5–6% of cases of unexplained IDA [8, 10–12].

In IBD patients, the initial therapeutic strategy for IDA should be based on the activity of the disease, the level of hemoglobin (Hb), and tolerance of the patient to oral iron [5,

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13]. In the recent European Crohn's and Colitis Organisation (ECCO) guidelines, oral iron may be used in IBD patients with mild anemia whose disease is clinically inactive and who have not previously been intolerant to oral iron [13]. Oral iron replacement therapy has long been the cornerstone of IDA treatment [6]; it is inexpensive, is simple to administer, and is not associated with life-threatening side effects. Unfortunately, absorption of oral iron is unpredictable in patients with active IBD due to the inflammatory inhibition of absorption as a consequence of the interaction between hepcidin and ferroportin [14]. In a recent study that evaluated whether inflammation as reflected by C-reactive protein (CRP) or interleukin 6 at initiation of treatment could predict the response to iron therapy, it was shown that Hb increases in the oral iron group were significantly lower in those with high CRP levels than in those with low CRP levels. With IV iron, response was fairly independent of inflammation. This further supports the assertion that IV iron can overcome the hepcidin block and explains why oral iron may not be as effective in patients with inflammation [15]. IBD patients develop IDA through increased iron loss from ongoing GI bleeding from the inflamed intestinal mucosa as well as from reduced iron absorption within the inflamed mucosa. Additionally, in approximately 50% of patients, oral iron ingestion is associated with GI side effects, leading to discontinuation of therapy, including abdominal pain, nausea, diarrhea, vomiting, and constipation [16–20]. Although its effect on IBD disease activity is unknown in humans, a number of animal IBD studies have shown that oral iron can lead to worsening of intestinal inflammation, increased disease activity, and increased oxidative stress [21]. To date, well-controlled trials evaluating the effect of oral iron on IBD disease activity have not been conducted.

Although there are no recent US IBD guidelines for IDA, ECCO recently published a guideline/consensus paper on IDA. Intravenous (IV) iron is recommended as the preferred route of administration in patients with clinically active IBD, previous intolerance to oral iron, and Hb less than 10 g/dL, as well as for patients who require erythropoiesis-stimulating agents. In patients with severe IDA requiring rapid replenishment of iron stores, or in patients intolerant of oral iron therapy, parenteral iron replacement allows rapid, safe, effective restoration of iron stores and bypasses the issue of poor intestinal absorption [5, 6, 22]. Despite clinical findings, widespread adoption of IV iron replacement has been slow, in part owing to historical adverse events of anaphylactic reactions associated with iron dextran formulations [6, 23, 24]. Newer, dextran-free iron carbohydrate complexes have been developed to avoid the issue of dextran-induced anaphylaxis and allow high-dose IV iron replacement while minimizing serious safety concerns [6, 25–27]. Although iron sucrose has been shown to be effective, it has dose- and rate-limiting factors that necessitate multiple infusions over

time to alleviate IDA, potentially consuming substantially more administrative and financial resources [4].

Ferumoxytol and ferric carboxymaltose (FCM) are two newer parenteral iron formulations registered in the USA that permit higher single doses to be delivered over shorter periods of time. Thus, they require fewer administrations to treat patients with IDA compared with other parenteral irons. Ferumoxytol was approved for use in the USA in 2009 with an indication for the treatment of IDA in adults with chronic kidney disease [28].

FCM is a stable type I polynuclear iron (III)–hydroxide carbohydrate complex that prevents the partial release of iron to serum ferritin, allowing the administration of high doses since this iron is available almost exclusively via reticuloendothelial processing [14, 29–31]. In the USA, FCM was approved in 2013 and is indicated for the treatment of IDA in adults who have intolerance, or have had an inadequate response, to oral iron therapy. It is also indicated for the treatment of IDA in non-dialysis-dependent chronic kidney disease [32]. This pooled analysis was performed to assess the safety and efficacy of FCM compared with the safety and efficacy of oral iron therapy and other IV iron therapies for IDA secondary to GI disorders.

Materials and Methods

Study Design

This was a post hoc analysis of primary data from four prospective, active-controlled trials that evaluated the efficacy and safety of FCM in patients with IDA resulting from a broad range of causes [33–35]. The original trial designs are summarized in Table 1. The data were re-evaluated by the investigators to identify patients whose principal cause of IDA was underlying GI disorders and to compare the efficacy and safety of FCM versus those of oral iron therapy and other IV iron therapies in patients with these disorders. The original study protocols were approved by institutional review boards at each center, trials complied with the Declaration of Helsinki, and all patients provided informed consent (NCT00703937 and NCT00704353 [33], NCT00704028 [34], and NCT00982007 [35]; <http://www.clinicaltrials.gov>).

Patient Selection

A list of preferred and verbatim terms from the GI section of the patient's medical history was generated. From these GI-related terms, conditions considered to be a likely cause of IDA were determined. Patients were identified and their data pooled if their medical history contained 1 or more of the terms. Patients with IDA related to bariatric surgery were

Table 1 Summary of four randomized controlled trials of ferric carboxymaltose (Injectafer®) versus oral or intravenous iron therapy for the treatment of iron-deficiency anemia [33–35]

Study	Barish et al. [33] (single-dose study) NCT00704353	Barish et al. [33] (multidose study) NCT00703937	Hussain et al. [34] NCT00704028	Onken et al. [35] NCT00982007
N	738 (<i>n</i> = 366, FCM; <i>n</i> = 369, SMC) ^a	708 (<i>n</i> = 343, FCM; <i>n</i> = 360, SMC) ^b	160 (<i>n</i> = 82, FCM; <i>n</i> = 78, DEX)	1011 (<i>n</i> = 503, FCM; <i>n</i> = 257, oral iron; <i>n</i> = 251, IVSC)
Population	Men and women 18–85 years of age with IDA	Men and women 18–85 years of age with IDA	Men and women ≥ 18 years of age with IDA and history of intolerance to or unsatisfactory response to oral iron	Men and women ≥ 18 years of age with IDA and history of unsatisfactory response to oral iron
Key inclusion criteria	Hb ≤ 12 g/dL and ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30%	Hb ≤ 11 g/dL; ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30%	Hb ≤ 11 g/dL; ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30%	Hb ≤ 11 g/dL; ferritin ≤ 100 ng/mL, or ≤ 300 ng/mL if TSAT ≤ 30%
Randomization	FCM 15 mg/kg or 750 mg (whichever was smaller) IV push injection at 100 mg/min on Day 0 versus SMC on Days 0–30 (oral or IV iron preparations)	FCM 15 mg/kg up to a single-dose maximum of 750 mg at 100 mg/min weekly until the calculated iron deficit dose had been administered (maximum total dose: 2250 mg) versus SMC on Days 0–42 (oral or IV iron preparations) All doses were calculated by the Ganzoni formula	FCM versus IV iron dextran (doses of both drugs were calculated by the Ganzoni formula) FCM 15 mg/kg up to a single-dose maximum of 750 mg on Days 0, 7, and 14; IV push injection weekly at 100 mg/min until the calculated iron deficit dose had been administered (maximum total dose: 2250 mg)	FCM 15 mg/kg up to a maximum of 750 mg on Days 0 and 7 versus oral iron 325 mg TID for 14 days or other IV standard-of-care iron preparation
Outcome measures	Clinical, laboratory, and safety data including adverse events Mean changes from baseline in hemoglobin and ferritin	Clinical, laboratory, and safety data including adverse events Mean changes from baseline in hemoglobin, ferritin, and TSAT	Incidence of serious TEAEs; change in Hb, ferritin, and TSAT from baseline to the maximum value observed for all patients	Mean change from baseline to maximum observed Hb value at any time between baseline and Day 35; mean change from baseline to maximum ferritin measurement any time between baseline and Day 35; mean change from baseline to each scheduled visit for Hb, ferritin, and TSAT levels; serious TEAEs
Timing of assessments	Clinical, laboratory, and safety data were collected on Days 0, 7, and 30 (or end of treatment)	Clinical, laboratory, and safety data were collected on Days 0, 7, 14, 28, and 42 (or end of treatment)	Laboratory data were collected at screening, baseline, and Days 0, 7, 14, 28, and 42; safety data were collected on Days 0, 7, 14, 28, and 42	Laboratory data were collected on Days 7, 14, and 35; safety data were collected on Days 7, 14, 35, 90, and 120

DEX iron dextran, Hb hemoglobin, FCM ferric carboxymaltose, IDA iron-deficiency anemia, IVSC intravenous standard-of-care iron therapy, SMC standard medical care (oral or IV iron therapy); TEAEs treatment-emergent adverse events, TSAT transferrin saturation

^aThree patients were not treated

^bFive patients were not treated

excluded; these data were published in a separate analysis [29].

Assessments

Efficacy measures included change in Hb, ferritin, and transferrin saturation (TSAT) from baseline to the maximum value observed for all patients. Change in Hb was stratified by baseline Hb, ferritin, and TSAT level. The number and percentage of patients reporting treatment-emergent adverse events (TEAEs) were summarized for each treatment group by overall incidence and relationship to study drug using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1.

Data Analysis

All efficacy analyses were performed on the modified intent-to-treat (mITT) population. The mITT population in three of the studies consisted of patients from the safety population who had two baseline Hb values and at least one postbaseline Hb assessment [33, 34]. In the fourth study, the mITT population consisted of patients from the safety population who received at least one dose of the randomly assigned study medication and had at least one postbaseline Hb assessment [35]. A post hoc subgroup analysis of changes in Hb, ferritin, and TSAT levels from baseline to maximum value between baseline and end of study or time of intervention was conducted with data from patients with IBD and those without IBD and with GI bleeding. All safety assessments were performed in the safety population, which

included all randomized patients who received at least one dose of study drug. Patient demographic data were summarized descriptively. The *P* value for change from baseline was calculated with a paired t-test, and the *P* value for the difference between FCM and the other comparators was calculated from a one-way analysis of variance. Correlation of baseline ferritin and TSAT values with change in Hb was calculated by Spearman rank-order correlation.

Results

A total of 191 patients (59 males and 132 females) were identified from the four trial datasets as having IDA secondary to GI disorders. The mean age of patients was 59.3 years, and the mean body mass index was 28.4 kg/m². GI-related conditions contributing to IDA included GI bleeding (62.8%), inflammatory bowel disease (27.7%), malabsorption (5.2%), celiac disease (4.7%), and others (6.8%). In all, 101 (52.9%) patients received FCM, 25 (13.1%) received oral iron (ferrous sulfate), and 61 (31.9%) received any other IV iron comparators, including iron sucrose, 32 patients (16.8%); iron dextran, 27 patients (14.1%); and ferric gluconate, two patients (1.0%) (Table 2). Four patients received other comparators and were not included in the analysis because results were confounded by the use of a combination of iron therapy and blood transfusions. The mean total doses of elemental iron were 1238 mg (FCM), 2703 mg (oral iron), 1086 mg (any other IV iron), and 943 mg (iron sucrose).

Table 2 Demographics and baseline characteristics by comparators

	FCM (<i>n</i> = 101)	Oral iron (<i>n</i> = 25)	Any other IV iron ^a (<i>n</i> = 61)	Iron sucrose (<i>n</i> = 32)
Sex, <i>n</i> (%)				
Male	26 (25.7)	8 (32.0)	24 (39.3)	12 (37.5)
Female	75 (74.3)	17 (68.0)	37 (60.7)	20 (62.5)
Race, <i>n</i> (%)				
Asian	0	0	1 (1.6)	0
Black	11 (10.9)	9 (36.0)	2 (3.3)	2 (6.3)
Caucasian	77 (76.2)	15 (60.0)	55 (90.2)	28 (87.5)
Hispanic	13 (12.9)	1 (4.0)	3 (4.9)	2 (6.3)
Mean age (SD), year	59.1 (18.9)	58.0 (13.4)	59.7 (18.3)	55.0 (18.1)
Mean weight (SD), kg	73.6 (19.3)	84.4 (19.5)	79.3 (21.4)	80.5 (25.1)
Mean BMI (SD), kg/m ²	27.2 (6.40)	30.5 (7.43)	28.7 (6.58)	28.8 (7.56)
Mean baseline Hb (SD), g/dL	9.7 (1.33)	10.6 (0.78)	9.6 (1.24)	9.5 (1.52)
Mean baseline ferritin (SD), ng/mL	29.1 (58.5)	39.8 (68.3)	11.4 (11.0)	10.0 (8.69)
Mean baseline TSAT (SD), %	11.3 (8.77)	14.6 (10.17)	9.0 (7.08)	8.9 (7.39)

BMI body mass index, FCM ferric carboxymaltose, Hb hemoglobin, SD standard deviation, TSAT transferrin saturation

^aAny other IV iron included two ferric gluconate patients, 27 iron dextran patients, and 32 iron sucrose patients

Patients in the FCM group received 1–3 administrations; the range in the other IV iron group was 1–20 administrations.

Efficacy

Hb, ferritin, and TSAT values increased significantly from baseline to maximum postbaseline values for all treatment groups ($P=0.001$), with the exception of ferritin values for patients in the oral iron group. Patients treated with FCM experienced significantly greater mean maximum Hb increases and absolute Hb values compared with patients treated with oral iron ($P=0.001$) (Table 3). Changes in Hb were similar with FCM and the other IV iron therapies. Patients in the FCM group had significantly greater (at least twofold in all comparisons) peak absolute ferritin values and increases from baseline compared with patients in the other treatment groups. There were no changes in ferritin values in the oral iron group. Compared with oral iron therapy and iron sucrose therapy, FCM treatment led to statistically significantly greater increases in TSAT values ($P=0.001$ and $P=0.002$, respectively) and to significantly greater absolute TSAT values.

To determine whether responses differed between patients with IBD and non-IBD causes of GI blood loss, we performed subgroup analyses of data from these two groups (Table 4). FCM led to significantly greater increases in Hb than oral iron in patients with IBD (1.9 vs. 0.6 g/dL [$P=0.028$]) as well as in those without IBD (2.1 vs. 0.7 g/dL

[$P=0.001$]). FCM also led to significantly ($P \leq 0.001$) greater increases in ferritin than oral iron and the other IV iron therapies in patients with IBD (FCM vs. oral iron: 474.3 vs. 12.6 ng/mL [$P=0.001$]; FCM vs. other IV therapies: 474.3 vs. 89.0 ng/mL [$P < 0.0001$]) and those without IBD (FCM vs. oral iron: 540.0 vs. 7.1 ng/mL [$P < 0.0001$]; FCM vs. other IV therapies: 540.0 vs. 275.5 ng/mL [$P < 0.0001$]).

Correlation of Baseline Hb, Ferritin, TSAT to Changes in Hb

The more severe a patient’s anemia was at baseline, the larger the increase in Hb in response to treatment. This correlation was not observed in patients receiving oral iron therapy (Table 5). Baseline ferritin and TSAT values had a statistically significant negative correlation with change in Hb (Spearman correlation coefficient $R = -0.43$ [$P < 0.001$] and $R = -0.55$ [$P < 0.001$], respectively). Lower ferritin values and lower TSAT values were associated with larger increases in Hb values, as shown in Figs. 1 and 2.

Safety

Total incidences in TEAEs were higher in the IV iron groups (approximately 50–60%) than in the oral iron group (32.0%; $P > 0.05$) and were lower for FCM (46.5%) than for other IV iron groups (55.7% for any other IV comparator, $P > 0.05$; 59.4% for iron sucrose, $P > 0.05$). Two events of hypophosphatemia were reported in the FCM

Table 3 Mean (SD) change in hemoglobin, ferritin, and transferrin saturation from baseline to maximum value between baseline and end of study or time of intervention

	FCM (n=101)	Oral iron (n=25)	Any other IV iron ^a (n=61)	Iron sucrose (n=32)
Hb, g/dL				
Baseline	9.7 (1.33)	10.6 (0.78)	9.6 (1.24)	9.5 (1.52)
Maximum value	11.8 (1.49)	11.4 (1.23)	11.6 (1.44)	11.4 (1.22)
Change to maximum value	2.2 (1.52)	0.8 (1.01)	2.0 (1.24)	1.9 (1.04)
P value*	–	0.001	0.391	0.329
Ferritin, ng/mL				
Baseline	29.1 (58.52)	39.8 (68.32)	11.4 (11.00)	10.0 (8.69)
Maximum value	567.3 (327.20)	39.8 (42.46)	281.2 (262.89)	167.9 (179.26)
Change to maximum value	538.2 (300.50)	0 (33.13)	269.8 (259.11)	157.9 (173.60)
P value*	–	0.001	0.001	0.001
TSAT, %				
Baseline	11.3 (8.77)	14.6 (10.17)	9.0 (7.08)	8.9 (7.39)
Maximum value	37.0 (15.38)	24.8 (13.44)	32.7 (19.00)	24.2 (14.29)
Change to maximum value	25.7 (14.34)	10.2 (14.27)	23.6 (17.94)	15.3 (11.56)
P value*	–	0.001	0.430	0.002

Iron sucrose is a subgroup of the any other IV iron comparator group

FCM ferric carboxymaltose, Hb hemoglobin; IV intravenous, NS, nonsignificant, SD standard deviation, TSAT transferrin saturation

*Pvalues refer to the comparison with FCM, from one-way analysis of variance

^aAny other IV iron included ferric gluconate (n=2), iron dextran (n=27), and iron sucrose (n=32)

Table 4 Mean (SD) change in hemoglobin, ferritin, and transferrin saturation from baseline to maximum value between baseline and end of study or time of intervention stratified by patients with inflammatory bowel disease and non-inflammatory bowel disease gastrointestinal bleeding

	FCM		Oral iron		Any other IV iron		Iron sucrose	
	IBD (<i>n</i> = 30)	Non-IBD GI bleeding (<i>n</i> = 57)	IBD (<i>n</i> = 7)	Non-IBD GI bleeding (<i>n</i> = 14)	IBD (<i>n</i> = 15)	Non-IBD GI bleeding (<i>n</i> = 46)	IBD (<i>n</i> = 12)	Non-IBD GI bleeding (<i>n</i> = 17)
Hb, g/dL								
Baseline	9.7 (1.3)	9.6 (1.4)	10.5 (0.9)	10.4 (0.9)	9.6 (1.2)	9.5 (1.2)	9.6 (1.3)	9.4 (1.7)
Maximum value	11.6 (1.3)	11.7 (1.6)	11.1 (1.2)	11.2 (1.4)	11.3 (1.3)	11.5 (1.6)	11.5 (1.1)	11.4 (1.3)
Change to maximum value	1.9 (1.5)	2.1 (1.4)	0.6 (0.7)	0.7 (1.0)	1.7 (1.1)	2.0 (1.3)	1.9 (1.1)	2.0 (1.1)
<i>P</i> value*	–	–	0.028	0.001	0.631	0.811	0.942	0.738
Ferritin, ng/mL								
Baseline	26.7 (46.7)	32.5 (68.7)	73.6 (115.0)	53.9 (87.9)	7.4 (4.5)	11.2 (11.1)	6.5 (4.3)	10.6 (5.9)
Maximum value	488.8 (225.8)	559.8 (250.3)	43.4 (39.5)	26.7 (17.7)	96.5 (64.5)	287.3 (247.9)	109.6 (62.9)	235.2 (163.9)
Change to maximum value	474.3 (218.5)	540.0 (247.7)	12.6 (8.2)	7.1 (10.1)	89.0 (62.9)	275.5 (249.5)	102.7 (60.8)	224.2 (165.6)
<i>P</i> value*	–	–	0.001	<0.0001	<0.0001	<0.0001	<0.0001	0.0004
TSAT, %								
Baseline	11.3 (8.8)	11.8 (9.1)	14.7 (10.1)	15.1 (9.8)	7.4 (4.9)	9.1 (7.5)	6.7 (3.9)	10.1 (8.9)
Maximum value	37.8 (17.4)	35.3 (12.8)	29.3 (11.3)	24.7 (14.6)	21.0 (15.6)	33.2 (19.4)	20.0 (9.7)	26.3 (15.2)
Change to maximum value	26.6 (16.1)	23.4 (11.6)	14.6 (14.8)	9.6 (15.7)	13.6 (11.7)	24.1 (19.1)	13.3 (7.2)	16.2 (13.0)
<i>P</i> value*	–	–	0.082	0.0004	0.009	0.827	0.009	0.032

Iron sucrose is a subgroup of the any other IV iron comparator group

FCM ferric carboxymaltose, GI gastrointestinal, Hb hemoglobin, IBD inflammatory bowel disease, IV intravenous; SD standard deviation, TSAT transferrin saturation

**P* values refer to the comparison with FCM, based on *t* test

Table 5 Mean (SD) change in hemoglobin from baseline to maximum value between baseline and end of study or time of intervention stratified by baseline hemoglobin level

	FCM		Oral iron		Any other IV iron		Iron sucrose	
	Female	Male	Female	Male	Female	Male	Female	Male
Patients with mild anemia (hemoglobin 11.0–11.9 g/dL, females; 11.0–12.9 g/dL, males) [36]								
<i>n</i>	10	6	6	3	5	1	4	1
Change to maximum value	1.0 (0.7)	1.7 (1.6)	0.6 (0.9)	1.4 (1.3)	0.9 (0.4)	1.0	0.9 (0.4)	1.0
<i>P</i> value*	–	–	0.336	0.788	0.774	–	0.796	–
Patients with moderate anemia (hemoglobin 8.0–10.9 g/dL, females and males) [36]								
<i>n</i>	55	19	11	5	29	20	13	8
Change to maximum value	2.2 (1.2)	2.2 (1.7)	0.8 (1.1)	0.6 (0.9)	1.9 (1.1)	2.2 (1.4)	1.9 (0.8)	2.0 (1.0)
<i>P</i> value*	–	–	0.001	0.061	0.266	> 0.999	0.396	0.763
Patients with severe anemia (hemoglobin < 8.0 g/dL, females and males) [36]								
<i>n</i>	9	1	0	0	2	3	2	3
Change to maximum value	3.6 (1.9)	5.9	–	–	3.0 (0.7)	3.3 (0.2)	3.0 (0.7)	3.3 (0.2)
<i>P</i> value*	–	–	–	–	–	–	–	–

FCM ferric carboxymaltose, IV intravenous, SD standard deviation

**P* values refer to the comparison with FCM, from one-way analysis of variance

Fig. 1 Correlation of baseline ferritin versus change in hemoglobin from baseline to maximum value between baseline and end of study or time of intervention in ferric carboxymaltose patients

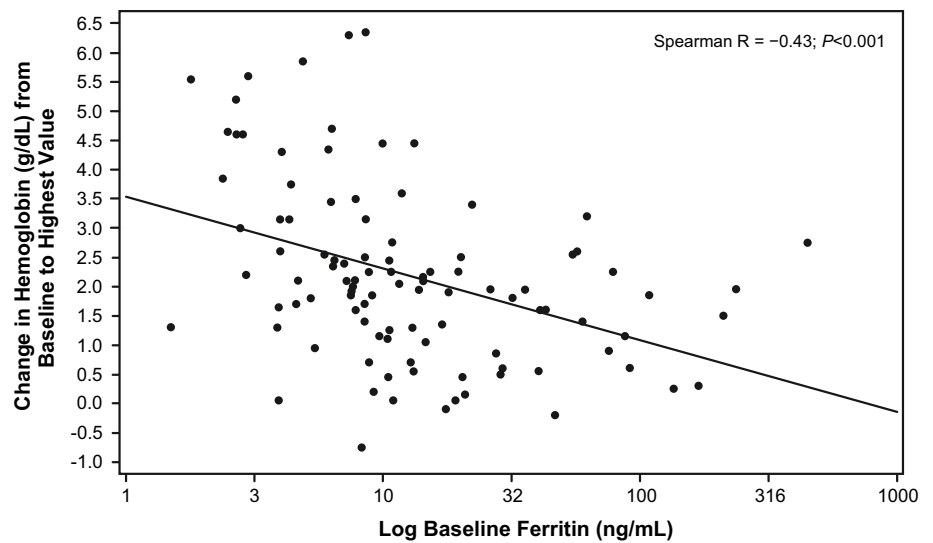
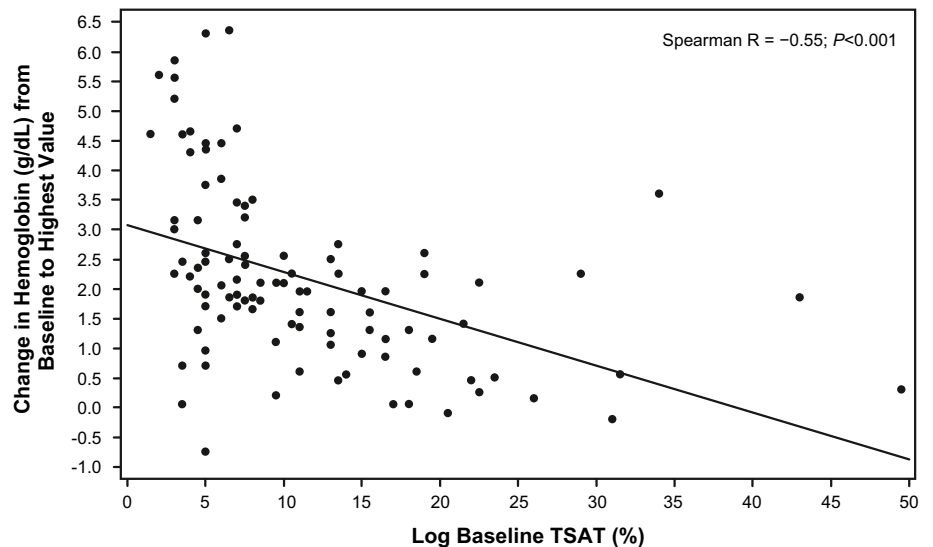


Fig. 2 Correlation of baseline TSAT versus change in hemoglobin from baseline to maximum value between baseline and end of study or time of intervention in ferric carboxymaltose patients. *TSAT* transferrin saturation



group, resolved over the course of the study, and were not associated with the development of a serious adverse event (SAE). The incidences of serious TEAEs were similar among the three IV iron groups and were lower with oral iron (Table 6). None of the SAEs was considered related to the study drug in patients receiving FCM; however, two SAEs were considered related to the study drug in two patients in the iron sucrose group (renal infarct and hypotension).

The incidence of drug-related TEAEs in the safety population is summarized in Table 7. No hypersensitivity reactions were reported in patients receiving FCM or oral iron but were reported in the other IV iron therapies and iron sucrose groups. Drug-related TEAEs occurred in the FCM (11.9%) and oral iron (12.0%) groups at less than half the frequency seen in the other IV iron therapies (26.2%) and iron sucrose (25.0%) groups.

As expected for this patient population, GI adverse events were the most commonly reported drug-related TEAEs (Table 7); interestingly, GI adverse events were more common in the iron sucrose group than with other therapies. GI disorders, particularly nausea and vomiting, were less common in patients receiving FCM than in patients receiving other IV iron therapies. Headache, hypotension, and hypersensitivity were also reported less frequently in patients receiving FCM than in patients receiving other IV iron therapies.

Few patients discontinued therapy because of adverse events in any of the treatment groups (FCM group, $n = 1$ [1.0%]; oral iron, $n = 0$; any other IV iron, $n = 3$ (4.9%); iron sucrose, $n = 1$ (3.1%).

Table 6 Serious TEAEs occurring in any treatment group (safety population)

TEAE, <i>n</i> (%)	FCM (<i>n</i> = 101)	Oral iron (<i>n</i> = 25)	Any other IV iron (<i>n</i> = 61)	Iron sucrose (<i>n</i> = 32)
Any adverse event	7 (6.9)	1 (4.0)	6 (9.8)	4 (12.5)
Gastrointestinal hemorrhage	2 (2)	0 (0)	1 (1.6)	1 (3.1)
Anemia	1 (1.0)	0 (0)	0 (0)	0 (0)
Iron-deficiency anemia	1 (1.0)	0 (0)	0 (0)	0 (0)
Leukocytosis	1 (1.0)	0 (0)	0 (0)	0 (0)
Crohn's disease	1 (1.0)	0 (0)	0 (0)	0 (0)
Volvulus	1 (1.0)	0 (0)	0 (0)	0 (0)
Death	1 (1.0)	0 (0)	0 (0)	0 (0)
Dehydration	1 (1.0)	0 (0)	0 (0)	0 (0)
Respiratory distress	1 (1.0)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	0 (0)	1 (4.0)	0 (0)	0 (0)
Coronary artery disease	0 (0)	0 (0)	1 (1.6)	0 (0)
Cellulitis	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Cerebrovascular accident	0 (0)	1 (4.0)	0 (0)	0 (0)
Transient ischemic attack	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Renal infarct	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Acute respiratory failure	0 (0)	0 (0)	1 (1.6)	0 (0)
Hypotension	0 (0)	0 (0)	1 (1.6)	1 (3.1)

IV intravenous, TEAE treatment-emergent adverse event

Discussion

In the present pooled analysis, Hb responses were greater in FCM-treated patients than in patients treated with oral iron and similar to Hb responses in patients treated with iron sucrose and other IV iron therapies, while requiring fewer administrations. Restoration of iron stores (as measured by ferritin) and increases in available iron (TSAT) were significantly greater in patients receiving FCM than in those receiving oral iron and iron sucrose.

Serum ferritin levels broadly reflect total body iron stores but should be interpreted with caution in patients with chronic inflammation, since ferritin is an acute-phase reactant. Iron regulation is closely related to inflammation, with hepcidin and interleukin 6 playing key roles in this regulatory process [37–39], particularly in the case of Crohn's disease [5, 40]. Nonetheless, absolute values for ferritin and changes from baseline in FCM-treated patients in this analysis were nearly fourfold those in iron sucrose-treated patients, suggesting a more robust replenishment of total body iron stores, necessary for long-term maintenance of Hb levels. In contrast, oral iron failed to produce any significant improvements in iron stores from baseline. Improvements in TSAT in the FCM-treated patients were also substantially greater than in the iron sucrose-treated patients.

A previous study of patients with IBD receiving FCM to treat IDA demonstrated improvements in Hb, ferritin, and TSAT values that were significantly greater ($P \leq 0.015$)

than in patients receiving iron sucrose [4]. In another study, patients with non-dialysis-dependent chronic kidney disease and IDA were randomly assigned to receive two 750-mg infusions of FCM in 1 week or iron sucrose 200 mg administered in up to five infusions in 14 days [41]. Increases from baseline to treatment Day 56 for Hb, ferritin, TSAT, and serum iron were superior for patients receiving FCM compared with patients receiving iron sucrose [41]. In the present study, patients with a lower baseline Hb value who received IV iron therapy had a greater increase in Hb from baseline than did patients with a higher baseline Hb value. Similar results were observed when ferritin and TSAT were correlated with Hb change from baseline. This may reflect the body's demand to achieve physiologic homeostasis. Similar analysis could not be conducted on the oral iron group because the number of patients was too small to be conclusive.

The safety results from our pooled analysis suggest that FCM can be safely administered to patients with GI-related IDAs and represent a favorable safety profile compared with that of iron sucrose or other IV therapies in the patient population studied. Our results are consistent with results from a recently reported systematic review and meta-analysis of FCM studies in patients with IBD by Aksan and colleagues [42], which also found FCM to be well tolerated in this population. Interestingly, the proportion of patients experiencing FCM-related TEAEs in our analysis (12%) was identical to the

Table 7 Drug-related TEAEs in ≥ 1% of patients in any treatment group (safety population)

TEAE, <i>n</i> (%)	FCM (<i>n</i> = 101)	Oral iron (<i>n</i> = 25)	Any other IV iron (<i>n</i> = 61)	Iron sucrose (<i>n</i> = 32)
Any adverse event	12 (11.9)	3 (12.0)	16 (26.2)	8 (25.0)
Diarrhea	2 (2.0)	1 (4.0)	2 (3.3)	1 (3.1)
Nausea	2 (2.0)	0 (0)	5 (8.2)	2 (6.3)
Arthralgia	2 (2.0)	0 (0)	2 (3.3)	2 (6.3)
Headache	1 (1.0)	0 (0)	3 (4.9)	0 (0)
Pruritus	1 (1.0)	0 (0)	1 (1.6)	0 (0)
Constipation	1 (1.0)	1 (4.0)	0 (0)	0 (0)
Vomiting	1 (1.0)	0 (0)	4 (6.6)	4 (12.5)
Abdominal discomfort	0 (0)	1 (4.0)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	1 (1.6)	0 (0)
Asthenia	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Chills	0 (0)	0 (0)	2 (3.3)	2 (6.3)
Peripheral edema	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Pain	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Hypersensitivity	0 (0)	0 (0)	4 (6.6)	2 (6.3)
Dizziness	0 (0)	0 (0)	2 (3.3)	1 (3.1)
Hypoesthesia	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Renal infarct	0 (0)	0 (0)	1 (1.6)	1 (3.1)
Cough	0 (0)	0 (0)	1 (1.6)	0 (0)
Dyspnea	0 (0)	0 (0)	1 (1.6)	0 (0)
Erythema	0 (0)	0 (0)	1 (1.6)	0 (0)
Rash	0 (0)	0 (0)	1 (1.6)	0 (0)
Hypotension	0 (0)	0 (0)	3 (4.9)	3 (9.4)
Thrombophlebitis	0 (0)	0 (0)	1 (1.6)	1 (3.1)

IV intravenous, TEAE treatment-emergent adverse event

proportion reported by Aksan and colleagues. It should be highlighted that the oral iron group may have had a lower adverse event profile due to the study design, given that patients included in the study by Onken et al. [35] were preselected for lack of a severe reaction (and lack of an adequate response) to oral iron. Also, TEAEs that were related to oral iron therapy would not have been counted as adverse events during the treatment phase, whereas all treatment-related TEAEs in the FCM group were considered new events. No hypersensitivity reactions were reported for patients receiving FCM in this analysis, although they were reported for some patients receiving other IV iron therapies (including iron sucrose), and were attributed to study drug treatment.

In this analysis, high-dose FCM was shown to be effective and well tolerated in the treatment of IDA in the GI setting. As such, FCM may be an appropriate alternative to more established parenteral iron therapies, allowing higher doses with each infusion and therefore fewer infusions to achieve repletion of iron stores and rapid Hb responses. Use of FCM may therefore lead to a cost savings, as well as greater convenience for both the patient and the treating physician.

Although this study suggests that FCM may be an appropriate IV iron therapy for the treatment of IDA in GI patients, there were some limitations to consider. As with any retrospective analysis, interpretation of the results is inherently limited by potential study selection bias and indirect comparisons in a pooled dataset from open-label studies that had different objectives and relatively small patient populations. The oral iron treatment group had a higher proportion of black patients than the other groups analyzed and had a higher mean baseline Hb level compared with the IV iron therapy groups. This may have been a result of study design, as the decision to proceed with oral or IV iron was left to the discretion of the investigator. This variation at baseline may have contributed to the fact that the oral iron group experienced the smallest change from baseline in Hb. Also, two of the studies in the current analysis used the Ganzoni formula for calculation IV iron doses and the other two did not. It is unclear whether differences in dosing methodologies across the studies could have affected our results.

Further, specific real-world and cost-effectiveness studies are required to determine the cost–benefit of IV iron therapies, as well as the real-world safety and efficacy of FCM

versus IV iron sucrose. The stability of the Hb response and clinical outcomes over time were not addressed in the current analysis. Finally, while use of the Ganzoni formula traditionally has been considered standard practice for calculation of a patient's total body iron deficit, several investigators have reported that the Ganzoni formula underestimates actual iron dose requirements in patients with IDA in IBD [4, 14, 43, 44]. Currently, no consensus exists on the most appropriate IV iron dose for patients with IDA; more studies are required to determine the optimal dosing for this patient population.

Conclusions

FCM is currently indicated in the USA for the treatment of IDA in adults when oral iron preparations are not tolerated or are ineffective. This analysis highlights that FCM is effective in patients with GI-related IDA and has a safety profile comparable to that of other IV iron agents.

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Compliance with ethical standards

Conflict of interest Gary R. Lichtenstein has served as a consultant to Luitpold Pharmaceuticals, Inc., and Jane E. Onken has served on a Steering Committee and Advisory Board for Luitpold Pharmaceuticals, Inc.

Statement of human rights All procedures performed involving human participants performed in the four studies included in this post hoc analysis were in accordance with the ethical standards of the institutional review boards at each center and with the 1964 Helsinki Declaration (NCT00703937 and NCT00704353, NCT00704028, and NCT00982007; <http://www.clinicaltrials.gov>).

Informed consent Informed consent was obtained for all individual participants included in the four studies in the current analysis.

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