

FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease

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BACKGROUND & AIMS: Iron deficiency anemia (IDA) is common in chronic diseases and intravenous iron is an effective and recommended treatment. However, dose calculations and inconvenient administration may affect compliance and efficacy. We compared the efficacy and safety of a novel fixed-dose ferric carboxymaltose regimen (FCM) with individually calculated iron sucrose (IS) doses in patients with inflammatory bowel disease (IBD) and IDA. **METHODS:** This randomized, controlled, open-label, multicenter study included 485 patients with IDA (ferritin <100 µg/L, hemoglobin [Hb] 7–12 g/dL [female] or 7–13 g/dL [male]) and mild-to-moderate or quiescent IBD at 88 hospitals and clinics in 14 countries. Patients received either FCM in a maximum of 3 infusions of 1000 or 500 mg iron, or Ganzoni-calculated IS dosages in up to 11 infusions of 200 mg iron. Primary end point was Hb response (Hb increase ≥2 g/dL); secondary end points included anemia resolution and iron status normalization by week 12. **RESULTS:** The results of 240 FCM-treated and 235 IS-treated patients were analyzed. More patients with FCM than IS achieved Hb response (150 [65.8%] vs 118 [53.6%]; 12.2% difference, $P = .004$) or Hb normalization (166 [72.8%] vs 136 [61.8%]; 11.0% difference, $P = .015$). Both treatments improved quality of life scores by week 12. Study drugs were well tolerated and drug-related adverse events were in line with drug-specific clinical experience. Deviations from scheduled total iron dosages were more frequent in the IS group. **CONCLUSIONS:** The simpler FCM-based dosing regimen showed better efficacy and compliance, as well as a good safety profile, compared with the Ganzoni-calculated IS dose regimen.

Keywords: Intravenous Iron; Crohn's Disease; Ulcerative Colitis.

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Iron deficiency and iron deficiency anemia (IDA) are frequent conditions in the general population¹ and present particularly often in patients with chronic diseases such as inflammatory bowel disease (IBD), rheumatoid ar-

thritis, chronic kidney disease, chronic heart failure, and cancer.^{2,3} Iron deficiency is an important cause of anemia, which in turn can trigger hospitalization and even mortality.⁴ Furthermore, anemia affects cardiac function and quality of life substantially.^{5,6} Iron deficiency even without anemia is associated with fatigue⁷ as well as impaired physical performance⁸ and cognitive function.^{4,6,9}

The main cause of a negative iron balance in patients with chronic diseases is impaired absorption and utilization of nutritional or orally administered iron.¹⁰ Proinflammatory cytokines up-regulate hepcidin, a key mediator in iron homeostasis that blocks the release of iron from enterocytes and macrophages and can lead to anemia of chronic disease.¹⁰ The shortage of iron can be aggravated by chronic blood loss leading to absolute iron deficiency and IDA. Management of iron deficiency by addressing iron availability and iron stores is critical. IBD is a model for such a condition with the prevalence of iron deficiency in IBD ranging from 36% to 90%.^{2,11}

Improvement of hemoglobin (Hb) and iron status (ie, serum ferritin and transferrin saturation) in anemic IBD patients can be achieved with systemic iron treatment^{12,13} and is associated with improved quality of life scores independent of changes in disease activity.⁶ In addition, iron deficiency is frequently associated with secondary thrombocytosis,¹⁴ adding a potential risk of thromboembolic events to these patients.¹⁵ Iron repletion and resolution of anemia may normalize the increased platelet counts.¹⁶

International guidelines for the management of anemia associated with IBD recommend intravenous iron replacement therapy as the preferred route of iron administration.¹⁷ Intravenous iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron supplements.^{13,17-19} Most clinical trials have used iron sucrose (IS) to evaluate efficacy and safety of intra-

Abbreviations used in this paper: CI, confidence interval; FCM, ferric carboxymaltose; Hb, hemoglobin; IBDQ, inflammatory bowel disease questionnaire; IDA, iron deficiency anemia; IS, iron sucrose; OR, odds ratio; SF-36, health survey short form; SD, standard deviation; TSAT, transferrin saturation.

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venous iron therapy. IS was effective in 50%–91% of IBD patients depending on the study criteria.² A recently reported randomized, controlled, multicenter study showed that intravenous IS treatment is superior to oral iron in correcting Hb and iron stores in IBD patients.¹⁸ In clinical practice, IS proved to be an effective and well-tolerated intravenous iron preparation.^{17,20,21}

A constraint of IS is the dose limitation of 200 mg iron per infusion because, in an IBD clinic, most anemic patients will have an iron deficit of 1000 mg or more. Thus, multiple infusions are required to replenish iron stores and correct IDA. Ferric carboxymaltose (FCM) is an intravenous iron preparation that can be administered in single doses of up to 1000 mg iron within 15 minutes. The efficacy and tolerability of FCM have been shown in various indications, including anemia associated with IBD,¹³ postpartum phase,²² heavy uterine bleeding,²³ and most recently in chronic heart failure.⁵

In current practice, the Ganzoni formula is used to calculate individual iron need.²⁴ However, this formula is inconvenient, prone to errors, inconsistently used in clinical practice, and underestimates iron requirements.¹³ Here, we evaluated whether a novel and simple dosing regimen of FCM is at least as effective and safe as the Ganzoni-calculated dosage of repeated IS infusions in anemic patients with mild or quiescent IBD.

Patients and Methods

Study Design and Patients

The study was designed as a randomized, controlled, multicenter, open-label trial testing a novel treatment regimen using FCM (Ferinject; Vifor Pharma, Glattbrugg, Switzerland) for noninferiority compared with the Ganzoni-calculated doses of IS (Venofer; Vifor Pharma, Glattbrugg, Switzerland) in patients with IBD and IDA. The study was conducted from October 2008 to December 2009 at 88 hospitals and clinics in 14 countries in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered at ClinicalTrials.gov (NCT00810030) and run after approval of the protocol and its amendments by the concerned local ethics committees and competent authorities. No conflicts of interests were disclosed to study participants in the informed consent form.

Patients with iron deficiency anemia (Hb 7–12 g/dL [female] or 7–13 g/dL [male] and ferritin <100 µg/L) and mild to moderate IBD (Crohn's disease [CD] with a Crohn's disease activity index [CDAI] <220 or ulcerative colitis [UC] with a colitis activity index [CAI] ≤7) or IBD in remission (CDAI <150 or CAI ≤4) were recruited. Further inclusion criteria were normal levels of vitamin B-12 and folic acid. Eligible patients had to be 18 years of age or older and to have signed informed consent. Females of child-bearing potential had to have a negative urine pregnancy test at screening and had to use an acceptable method of birth control during the study and for up to 1 month after the last dose of the study drug. Patients with intravenous or oral iron treatment or blood transfusions within 4 weeks prior to screening or history of erythropoietin treatment were excluded. Further exclusion criteria comprised chronic alcohol abuse; chronic liver disease or increase of transaminases more than 3 times above the normal upper range limit; presence of portal

hypertension with esophageal varices; known hypersensitivity to the study drug; history of acquired iron overload; myelodysplastic syndrome; pregnancy or lactation; known active infection; clinically significant overt bleeding; active malignancy or chronic renal failure; surgery with relevant blood loss (Hb decrease <2 g/dL) in the 3 months prior to screening or planned surgery within the following 3 months; known human immunodeficiency virus; hepatitis B or hepatitis C virus infection; significant cardiovascular disease; body weight <35 kg; and participation in any other interventional study within 1 month prior to screening.

Randomization

Patients were randomized 1:1 to each of the treatment arms according to a predefined, computer-generated list and stratified by gender and disease (CD/UC) as provided via sequentially numbered randomization envelopes by data management, PAREXEL International GmbH. Both participants and physicians were aware of which treatment was being administered.

Treatment Schedule

The selection of FCM total dosages was based on predefined cut-offs for baseline Hb levels and body weight (Table 1). FCM was administered in single, once weekly infusions of 1000 mg or 500 mg iron over at least 15 minutes on day 1 and, if needed, days 8 and 15. Patients with a body weight <67 kg received a maximum of 500 mg iron per infusion. The IS regimen was calculated for each patient individually by the Ganzoni formula (total iron dose = [body weight × (target Hb – actual Hb)] × 2.4 + iron storage depot) and comprised up to 11 infusions of 200 mg iron over at least 30 minutes given up to twice weekly (target Hb level 15 g/dL, iron storage depot 500 mg).

Outcome Measures

The primary end point was the number of Hb responders as defined by an Hb increase ≥2 g/dL at week 12 compared with baseline levels. Secondary efficacy end points comprised the proportions of patients achieving normalization of Hb (≥12 g/dL in female, ≥13 g/dL in male patients), transferrin saturation (TSAT; 20%–50%), and ferritin (≥100 µg/L) at week 12 as well as repeated measure analyses of changes in Hb, TSAT, and ferritin from baseline to subsequent visits.

Further secondary parameters were the proportion of patients who were no longer anemic or achieved an Hb increase ≥2 g/dL, who were no longer anemic and achieved ferritin >100 µg/L, as well as changes in health-related quality of life, which was assessed using the Health Survey Short Form (SF-36), version 2,²⁵ and Inflammatory Bowel Disease Questionnaire (IBDQ) scores²⁶ from baseline to week 12.

Follow-up and Safety Evaluation

Patients in both groups were evaluated at weeks 1, 2, 4, 8, and 12. At each visit, blood tests were performed, and adverse

Table 1. Total Iron Dose With the FCM Dose Regimen

Hb (g/dL)	Body weight <70 kg	Body weight ≥70 kg
≥10	1000 mg	1500 mg
7–10	1500 mg	2000 mg

NOTE. Total dosage was administered in single infusions of 500 mg or 1000 mg iron as FCM. For patients with a body weight <67 kg, single doses of 500 mg were given.

events, disease activity index, and concomitant medication were recorded. Disease activity index was calculated without consideration of Hb or hematocrit levels. Adverse events were considered treatment emergent if they occurred after the first study drug administration. Relationship to treatment was rated as certain, probable, possible, unlikely, or not related, and intensity was rated as mild, moderate, or severe. Pregnancy and symptomatic study drug overdose were reported as serious adverse events. Safety stopping rules for premature discontinuation included Hb <7 g/dL, Hb >18 g/dL (male) or 16 g/dL (female), ferritin >800 µg/L, TSAT >50%, and liver function tests above 3 times the upper limit of normal.

Cost-effectiveness Analysis

Within-trial cost-effectiveness analysis from a third party payer perspective was performed for Switzerland, one of the countries participating in the trial. Administration, material, and drug costs were taken into account. Clinical effectiveness was estimated as the response rate difference between treatment groups (the primary end point). Cost estimation was based on Swiss public drug prices (FCM: United States dollar [USD] 37.89; IS: USD 31.01; prices per 100 mg)²⁷ and Swiss national fee-for-service reimbursement tariffs for outpatient services (Tarmed).²⁸ Unit costs were converted into USD using an exchange rate of 1.07 Swiss Francs/USD (average rate for the first quarter of 2011). Robustness of results was confirmed in deterministic sensitivity analysis.

Statistical Analysis

Difference in the primary end point between the treatment groups was evaluated by a 1-sided Wilson score test with a 97.5% confidence interval (CI), and the sample size was calculated to achieve a power of 90% ($\beta = .10$). Noninferiority was concluded if the lower margin of the confidence interval was $\geq -7\%$. Other statistical tests were 2-sided with a significance level of 5% and 95% confidence intervals (95% CI) unless otherwise specified. Logistic regression was applied when analyzing secondary end points. Analysis of (co)variance was used for continuous variables and Fisher exact tests for proportions.

Descriptive statistics comprised mean and standard deviation (SD). Missing data were treated as missing, and only observed cases were used for analysis. Data from 3 analysis sets are reported. The safety set comprised all randomized patients who received at least 1 study medication (analysis as treated). The full analysis set included patients who received at least 1 study dose and attended at least 1 postbaseline visit (analysis as randomized based on observed cases). The per-protocol set comprised patients without major protocol deviations and 100% ($\pm 10\%$) adherence.

Results

Patient Characteristics

A total of 880 patients were screened; 485 were randomized. Most common screening failures were not meeting the inclusion or exclusion criteria (361 patients, 91.4%). Two patients did not participate because of the projected number of IS injections. Details of patient disposition to treatment arms and populations analyzed are summarized in a CONSORT diagram (Figure 1). No differences were observed in patient demographics, type and history of IBD, and laboratory measures between the treatment groups at baseline (Table 2).

Treatment Characteristics

Patients treated with FCM received a mean \pm SD total iron dose of 1377 ± 381 mg, and patients treated with IS received 1160 ± 316 mg. The difference resulted from variations between the standardized IS and FCM dose regimens, and did not reflect a baseline difference in iron deficits (calculated iron deficits were 1245 ± 239 mg in the FCM and 1207 ± 253 mg in the IS group). Fewer infusions were required in the FCM group compared with the IS group (2.1 ± 0.6 vs 5.8 ± 1.6 infusions, respectively; $P < .001$). Deviations from the scheduled dose were less frequent in the FCM group (3.7% vs 15.1%, respectively, $P < .001$). Full adherence to treatment regimen was achieved more often in the FCM group (92.5% vs 79.1%, respectively, $P < .001$).

Response Rate at Week 12: Primary End Point

Hb increase ≥ 2 g/dL at week 12 was achieved in 150 (65.8%) patients in the FCM group and 118 (53.6%) patients in the IS group (full analysis set, 95% CI for difference: 3.07–20.97; $P = .004$) with similar results in the per protocol set (Table 3). The FCM group was shown to be more likely to achieve nonanemic state or an Hb

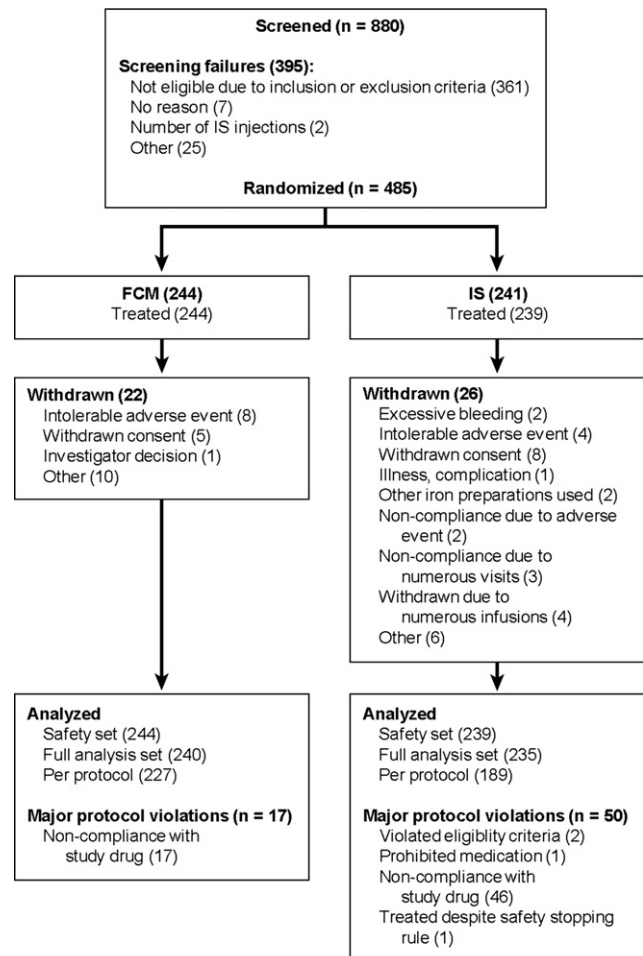


Figure 1. Patient flow diagram.

Table 2. Patient Characteristics at Baseline: Safety Set

	FCM (n = 244)	IS (n = 239)
Demographics		
Median age, y (range)	39.5 (18.0–81.0)	38.0 (18.0–78.0)
Female, n (%)	146 (59.8)	138 (57.7)
Disease history and status		
Crohn's disease, n (%)	86 (35.2)	74 (31.0)
Median duration of Crohn's disease, mo (range)	68.3 (1.3–503.3)	65.5 (0.3–347.6)
Mean CDAI (SD)	97.5 (61.2)	84.5 (61.7)
Median duration of UC, mo (range)	49.9 (0.3–320.9)	41.1 (0.2–407.2)
Mean CAI (SD)	3.7 (2.1)	3.2 (2.2)
Median duration of anemia, mo (range)	6.4 (0.0–320.9)	9.1 (0.0–264.9)
Laboratory values		
Mean Hb, g/dL (SD)	10.1 (1.5)	10.3 (1.5)
Mean % TSAT (SD)	9.0 (9.1)	9.6 (9.5)
Mean ferritin, $\mu\text{g/L}$ (SD)	14.8 (24.6)	17.8 (27.6)
Mean C-reactive protein, mg/L (SD)	7.3 (9.1)	8.0 (10.6)
Prior and concomitant medication (in $\geq 5\%$ patients)		
Glucocorticosteroids, n (%)	48 (19.7)	55 (23.0)
5-ASA derivatives, n (%)	161 (66.0)	142 (59.4)
Azathioprine, n (%)	42 (17.2)	44 (18.4)
TNF- α antagonists, n (%)	21 (8.6)	18 (7.5)

NOTE. No statistically significant differences between groups. CAI, colitis activity index; CD, Crohn's disease; CDAI, Crohn's disease activity index; TNF, tumor necrosis factor; UC, ulcerative colitis.

increase ≥ 2 g/dL than the IS group (full analysis set; 191 [83.8%] vs 167 [75.9%] of patients; odds ratio [OR], 1.67; 95% CI: 1.04–2.67; $P = .033$). The lower limits of the confidence intervals for treatment difference between response rates in the FCM and the IS group were above zero and clearly exceeded the predefined noninferiority margin of -7% . The confidence interval being entirely in favor of FCM confirms the superior efficacy of the FCM dosing regimen.

Secondary End Points

Normal Hb (gender specific ≥ 12 or ≥ 13 g/dL), normal TSAT (20%–50%), normal ferritin (≥ 100 $\mu\text{g/L}$),

and normal Hb combined with normal ferritin were achieved significantly more often by patients in the FCM group (Table 4). Repeated measures analyses showed significantly stronger increases in Hb (from week 2 onward), TSAT, and ferritin (at all time points) in the FCM group (Figure 2). Analysis of the SF-36 and IBDQ scores that were adjusted for gender and disease status at baseline scores showed improvements in all dimensions from baseline to week 12 in both treatment groups (Table 4).

Safety

Both treatment regimens were well tolerated, and most adverse events were mild or moderate. Overall, the most common adverse events were nasopharyngitis (21 patients [4.3%]) and worsening of UC (20 patients, [4.1%]). The frequency of treatment-related adverse events was comparable between the 2 groups ($P = .413$; Table 5). One treatment-related serious adverse event (pulmonary embolism) was reported in the FCM group. Skin and subcutaneous tissue disorders such as rash, dermatitis, and pruritus that were related to the study drug were reported in 9 (3.7%) patients of the FCM and 2 (0.8%) patients of the IS group ($P = .063$). Five patients of the FCM group discontinued the study because of such events. Overall, 7 infusion site reactions were observed: 1 (0.4%) in the FCM group and 6 (2.5%) in the IS group. No true hypersensitivity reactions were reported.

The most common treatment-related adverse events were transient hyperferritinemia and transient hypophosphatemia. Mean serum phosphate levels in the FCM group decreased from baseline (1.12 ± 0.22 mmol/L) to week 2 (0.69 ± 0.24 mmol/L) and returned to normal between week 4 and week 12 (1.11 ± 0.23 mmol/L). No apparent differences in other laboratory parameters were observed between the 2 treatment groups. Mean platelet counts in the overall population decreased from 359 G/L at baseline to 298 G/L at week 4 and remained at this level. Leukocyte counts and C-reactive protein levels were stable throughout the study period in both groups.

Table 3. Response Rates at Week 12

	Full analysis set		Per protocol set	
	FCM (n = 240 ^a)	IS (n = 235 ^a)	FCM (n = 227 ^a)	IS (n = 189 ^a)
Hb increase ≥ 2 g/dL (primary end point)				
Responder, n (%)	150 (65.8)	118 (53.6)	144 (66.1)	98 (54.1)
% difference between FCM and IS	12.15		11.91	
95% CI for difference	3.07–20.97		2.28–21.31	
P value	.004		.008	
Hb increase ≥ 2 g/dL or normal Hb^b				
Responders, n (%)	191 (83.8)	167 (75.9)	184 (84.4)	137 (75.7)
% difference between FCM and IS	7.86		8.71	
95% CI for difference	0.43–15.25		0.88–16.66	
P value	.019		.014	

^aObserved cases were used for analysis.

^bGender-specific normal Hb: ≥ 12 g/dL (females), ≥ 13 g/dL (males).

Table 4. Secondary End Point Response Rates at Week 12 for the Full Analysis Set

	FCM (n = 240 ^a)	IS (n = 235 ^a)	P value (OR, 95% CI)
Normal Hb ^b			
Responders, n (%)	166 (72.8)	136 (61.8)	.015 (1.65, 1.10–2.46)
Normal TSAT (20%–50%)			
Responders, n (%)	117 (52.7)	76 (36.4)	<.001 (2.05, 1.37–3.06)
Normal ferritin (≥100 μg/L)			
Responders, n (%)	96 (42.5)	60 (27.3)	.001 (1.95, 1.30–2.92)
Normal Hb ^b and ferritin (≥100 μg/L)			
Responders, n (%)	69 (31.1)	36 (16.7)	<.001 (2.23, 1.40–3.53)
SF-36 physical component summary			
Mean at baseline (SD)	44.17 (7.36)	44.98 (7.23)	
Mean change from baseline (SD)	3.88 (6.77)	2.64 (7.14)	.157
P value for change from baseline	<.001	<.001	
SF-36 mental component summary			
Mean at baseline (SD)	40.02 (11.04)	41.30 (11.70)	
Mean change from baseline (SD)	5.91 (10.74)	5.56 (10.36)	.583
P value for change from baseline	<.001	<.001	
IBDQ total score			
Mean at baseline (SD)	150.8 (35.2)	152.7 (34.4)	
Mean change from baseline (SD)	21.1 (32.3)	19.7 (28.8)	.872
P value for change from baseline	<.001	<.001	

^aObserved cases were used for analysis.

^bGender specific normal Hb: ≥12 g/dL (females), ≥13 g/dL (males).

Cost-effectiveness Analysis

Treatment cost per single iron dose for FCM (mean, 656 mg iron) and IS (mean, 200 mg iron) were USD 311 and USD 154, respectively. Because more infusions were required in the IS group, total treatment costs

for FCM over the whole study period were lower than those for IS (USD 653 vs USD 891, respectively) (Supplementary Table 1). This result implied dominance of FCM because of both a saving of USD 238 per patient and a 12% higher response rate.

In univariate sensitivity analysis, dominance of FCM over IS was maintained under unfavorable assumptions for each parameter (Supplementary Figure 1). The most influential parameter was the drug cost of FCM, followed by the total number of IS infusions and administration cost per IS infusion.

Discussion

This study is the largest study to date addressing IDA in IBD. It showed that patients with IDA secondary to IBD responded significantly better to FCM with its simplified dose regimen than to the Ganzoni-calculated IS dose regimen. The FCM regimen resulted in Hb normalization in 73% of patients, and almost twice as many FCM-treated patients responded with normalization of both Hb and ferritin than in the IS group (31% vs 17%). Disease-related (IBDQ) physical and mental quality of life (SF-36) improved with both preparations over the 12-week study period. Both treatments were well tolerated, and safety profiles matched the clinical experience with FCM and IS.³

Although the study was designed as a noninferiority study, the CI range was entirely above zero (for full analysis set and per protocol set), thus providing clear evidence of superiority of the FCM-based regimen. Notably, patients in the FCM group received 217 mg (18.7%) more iron than patients in the IS group. It cannot be distinguished whether the observed superiority results only from the higher dose associated with the FCM regimen or

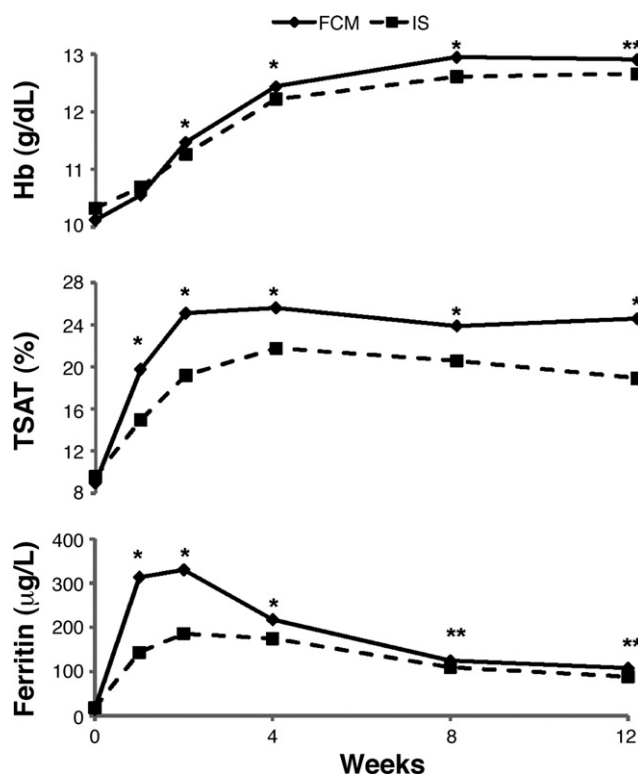


Figure 2. Time courses of patients' Hb, TSAT, and ferritin levels show earlier and consistently better improvement of Hb and iron status with the FCM regimen compared with the IS regimen.

* $P < .001$ and ** $P \leq .015$ for changes vs baseline.

Table 5. Drug-Related Adverse Events for the Safety Set

No. (%)	FCM (n = 244)	IS (n = 239)	P value
Any adverse event	34 (13.9)	27 (11.3)	.413
Severe adverse event ^a	1 (0.4)	0 (0.0)	1.0
Withdrawn because of adverse event	7 (2.9)	2 (0.8)	.176
Most common adverse events (>1% of patients)			
Hyperferritinemia	7 (2.9)	1 (0.4)	.068
Hypophosphatemia	6 (2.5)	0 (0.0)	.030
Rash	4 (1.6)	0 (0.0)	.124
Headache	3 (1.2)	1 (0.4)	.624
Iron overload	1 (0.4)	3 (1.3)	.368

^aSerious adverse event of pulmonary embolism.

from better efficacy of FCM itself as suggested by the rapid uptake of FCM in the bone marrow.²⁹ Improved erythropoietic bioavailability of FCM has also been suggested in another head-to-head comparison.^{30,31} The increase in available iron (as measured by TSAT) was constantly higher in the FCM group over the entire study period (Figure 2). The early and sustained superior response to the FCM regimen also confirms the availability of iron after administration of high doses in patients with chronic disease and dispels concerns that iron might be retained in iron storage compartments.^{6,32}

Dosing of FCM comprised 1 to 3 infusions of 500 or 1000 mg iron compared with up to 11 infusions of 200 mg iron with the Ganzoni-calculated IS regimen. Total FCM dosage can be easily identified from a simple 4-field grid based on predefined cut-offs of Hb and body weight (Table 1). Full adherence to the treatment regimen was higher in the FCM group. Seven patients of the IS group had to be withdrawn for noncompliance because of the numerous repeat visits required in this treatment group (Figure 1).

The lower number and shorter duration of infusions needed with FCM resulted in better cost-effectiveness in our analysis. Higher drug costs for FCM were outweighed by higher administration costs for IS. Because FCM is not yet available in the United States, we were unable to perform such analysis from the United States payers' perspective. Cost-effectiveness will depend on local drug and administration costs for FCM and IS.

Previous studies have suggested that the Ganzoni formula, currently the gold standard to calculate the iron deficit, underestimates actual iron requirements.¹³ In this study, even in the FCM group that received approximately 200 mg more iron, repletion of iron stores as recommended by international guidelines (ie, ferritin >100 µg/L)¹⁷ was achieved only for 31% of patients, although anemia was resolved in 73%. This indicates that current treatment approaches still underestimate iron needs in patients with IBD. Notably, a recently published retrospective analysis of 88 patients showed that insufficient iron repletion (ferritin <100 µg/L) relates to rapid recurrence of iron deficiency within 4 months and consequent reinitiation of iron treatment.²⁰ Accordingly, the observations in our large and prospective study highlight the need for complete iron repletion and the necessity for close follow-up in patients with high iron needs.¹⁷ Furthermore, maintenance iron ther-

apy may be required to compensate for the IBD-associated negative iron balance. This is the primary objective of the recently completed FERGI-MAIN study (NCT00810004), which is currently being analyzed.

Both treatments were well tolerated with adverse event profiles comparable with former reports on the use of FCM and IS. Drug-related reactions were mainly mild to moderate. Injection site reactions were more often reported in the IS group, possibly because of the higher number of infusions required for administration of the IS total dosage. There was a trend for more skin and subcutaneous tissue reactions in the FCM group; however, no true hypersensitivity reactions were observed. Hyperferritinemia and hypophosphatemia were transient and without clinical symptoms. The mechanism of the decrease in mean serum phosphate levels with the FCM regimen is unknown. It could be due to increased levels of fibroblast growth factor 23,^{33,34} a hormone that reduces renal phosphate absorption. Alternatively and similar to the refeeding syndrome, an anabolic effect on skeletal muscles (that may be myoglobin depleted because of iron deficiency), may lead to a shift of serum phosphate into the intracellular compartment.³⁵ It has been speculated that phosphate may bind directly to FCM via electrostatic interaction and thus contribute to the observed hyperphosphatemia.³⁶ However, this explanation is in contrast with the time point of the observed nadir of the hypophosphatemia (2–3 weeks after intravenous iron injection) and the half-life of FCM (7–12 hours).²⁹

Neither FCM nor IS was associated with an increase in leukocyte count or C-reactive protein. Intravenous iron replacement did not affect disease activity. Overall, we observed a reduction in disease activity scores, although disease activity increased in a few patients with UC. Thrombocyte counts decreased in both groups, which is in accordance with other studies.¹⁶

In conclusion, the novel and simplified fixed-dose ferric carboxymaltose regimen, depending on weight and baseline Hb and comprising a maximum of 3 infusions, showed superior efficacy compared with the Ganzoni-calculated IS dosing currently used in clinical practice. The FCM dosing regimen has been well tolerated, and the lower number of infusions increases the convenience and cost-effectiveness of intravenous iron repletion in patients with iron deficiency.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.06.005.

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Conflicts of interest

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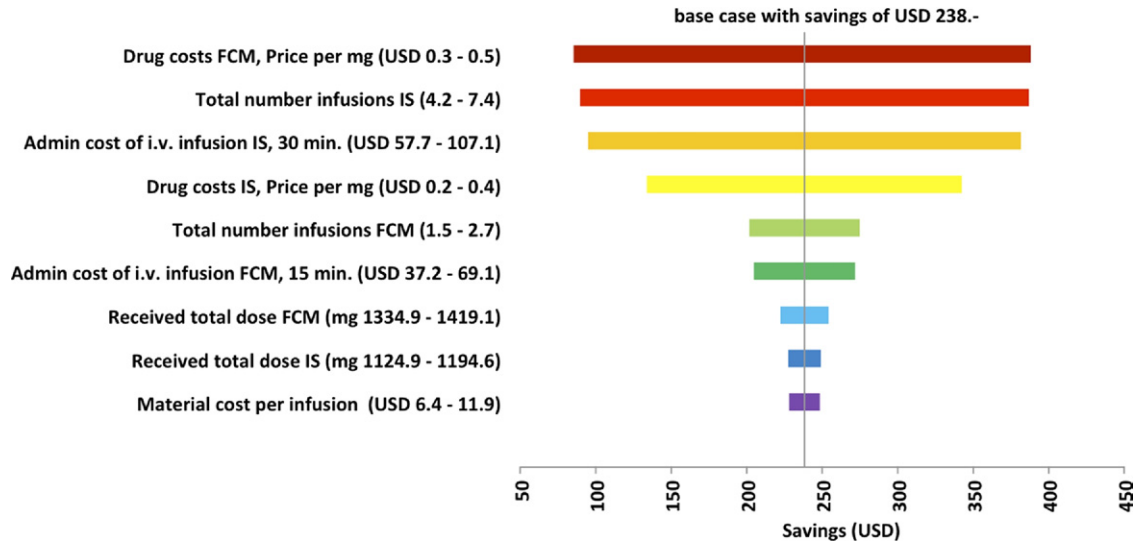
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Supplementary Table 1. Total Treatment Costs per Single Dose and Over the Entire Study Period

	FCM	IS
Drug costs per single dose	248.46	62.01
Material costs per single dose	9.19	9.19
Administration costs per single dose	53.12	82.39
Total treatment costs per single dose	310.77	153.59
Drug costs over study period	521.77	359.63
Material costs over study period	19.30	53.32
Administration costs over study period	111.55	477.86
Total treatment costs over study period	652.63	890.81
Difference between FCM and IS		238.18

NOTE. Costs are shown in US dollars.

Calculation is based on a duration of administration of 15 minutes for FCM and 30 minutes for IS.



Supplementary Figure 1. Tornado diagram showing impact of parameter uncertainty. In univariate sensitivity analysis, drug prices, administration costs, and material costs were varied by $\pm 30\%$ because no confidence intervals were available for these parameters. The total number of infusions and the received total doses were varied on the basis of their standard deviation and confidence intervals, respectively. USD, US dollar.