Effects of Ferric Carboxymaltose vs Ferumoxytol on Hypophosphatemia in Patients with Iron Deficiency Anemia due to Gastrointestinal Disorders

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Background

- Iron deficiency anemia (IDA) is common in patients with gastrointestinal (GI) disease, as a result of chronic blood loss, malnutrition, or malabsorption of iron, often coexisting with impaired utilization of endogenous iron in patients with chronic inflammation, such as inflammatory bowel disease (IBD)[1,2]
- Intravenous (IV) iron is a commonly used treatment for patients with GI disorders who are unable to tolerate or adequately respond to oral iron
- A growing number of case reports have described treatment-emergent hypophosphatemia following IV iron administration as a potential safety consideration, and a warning about symptomatic hypophosphatemia in patients at risk for low serum phosphate was recently added to the FDA prescribing information for one IV iron product, ferric carboxymaltose (FCM)[3,4,5]
- Although hypophosphatemia may have clinical consequences, its diagnosis may be missed due to initial nonspecific symptomatic presentation e.g., generalized weakness and fatigue[6]
- Many patients with GI disorders require repeated courses of treatment with IV iron and might be at a higher risk for hypophosphatemia[2]

Objective

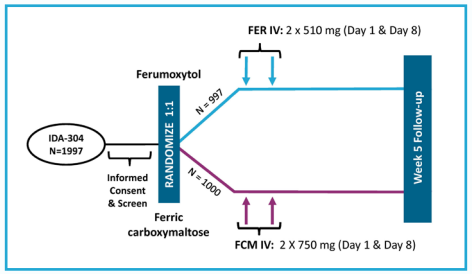
- To evaluate the effects of IV iron treatment on the incidence of hypophosphatemia in the subgroup of patients with IDA due to GI disorders who participated in a Phase 3 clinical trial that compared two IV iron preparations for the treatment of patients with IDA of any etiology and a history of unsatisfactory response to, or intolerance of oral iron

Methods

Study Design

- Post-hoc subgroup analysis of data from patients with IDA due to GI disorders enrolled in the Phase 3, Randomized, Multicenter, Double-Blind, Safety Study of Ferumoxytol (FER) Compared to Ferric Carboxymaltose (FCM) for the Treatment of Iron Deficiency Anemia (FIRM Trial, NCT026949784)[7]

Figure 1. Study Design



- Patients were randomized 1:1 to receive FER (two 510 mg IV doses) or FCM (two 750 mg IV doses) on Days 1 and 8. Both drugs were administered according to their respective FDA-approved dosing regimens **(Figure 1)**
- Serum phosphate and other clinical laboratory values were measured at Baseline and at Days 8 (prior to dose 2), 15, and 35
- Data were extracted for post-hoc analyses from patients whose primary cause of IDA was attributed by investigators to an underlying GI disorder

Results

Participants and Baseline Characteristics

- A total of 583 of 1,997 (29.2%) randomized patients who received at least 1 dose of study drug in the Phase 3 clinical trial had IDA due to an underlying GI disorder
- Among the most common comorbid GI conditions were: gastroesophageal reflux disease (30.1%), history of bariatric surgery (19.8%), IBD (12.9%), ulcer-related condition (8.4%), GI bleeding-related condition (4.6%), with some patients having multiple conditions
- Most baseline demographics were evenly distributed between the FER and FCM treatment groups of the GI subgroup
- Baseline serum phosphate mean values were similar between treatment groups (FCM 3.7 ± 0.5 and FER 3.7 ± 0.6 mg/dL) (**Table 1**)

Table 1. Baseline Characteristics of GI Subgroup

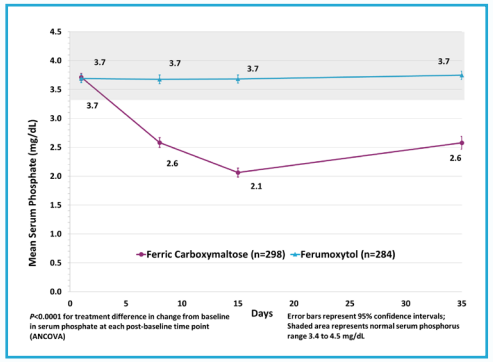
	FER n = 284	FCM n = 298	*P**
	n (%)		
Sex female	195 (74.5)	222 (68.7)	0.141
Race			0.958
White	243 (85.6)	253 (84.9)	
Black or African American	29 (10.2)	34 (11.4)	
Asian	7 (2.5)	6 (2.0)	
Other or Unknown	5 (5)	5 (7)	
GFR < 60 mL/min/m²	57 (20.1)	45 (15.1)	0.127
	mean (SD)		
GFR, mL/min/m²	82.9 (27.6)	87.5 (27.0)	0.045
Hgb, g/dL	10.6 (1.6)	10.5 (1.6)	0.569
Age, years	57.3 (17.0)	55.3 (16.3)	0.156
Weight, Kg	81.4 (20.6)	87.3 (27.3)	0.003
Phosphate, mg/dL	3.7 (0.5)	3.7 (0.5)	0.649

*Students t-test or Fisher's exact test

Changes in Serum Phosphate Levels

- In the FER group, mean serum phosphate levels remained unchanged from baseline throughout the study period
- In the FCM group, mean serum phosphate levels decreased significantly at each time point compared with baseline and to the FER group (all *P*<0.0001) **(Figure 2)**

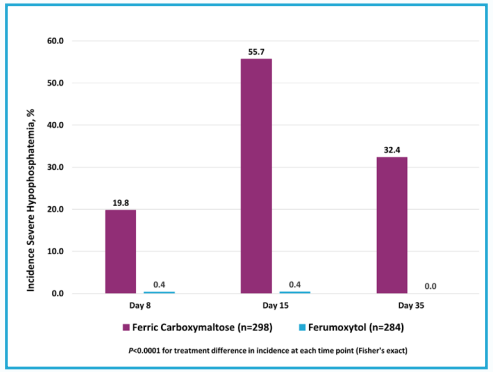
Figure 2. Serum Phosphate Levels



Incidence of Severe Hypophosphatemia

- The incidence of treatment-emergent severe hypophosphatemia (CTCAE Grade 3; <2mg/dL)[8] at any time during the study was higher in the FCM group compared with the FER group (58.8% vs. 0.7%, *P*<0.0001); unadjusted odds ratio [OR] 195.9, 95% CI 47.8 to 802.5; controlling for baseline characteristics [weight, GFR, baseline phosphate] OR 418.4, 95% CI 57.5 to 3044.1) (**Figure 3**)

Figure 3. Incidence of Treatment-Emergent Severe Hypophosphatemia (Serum Phosphate <2 mg/dL)



- This increased rate was observed at each time point (*P*<0.001), peaking in frequency at week 2, and remaining at 32.4% for FCM vs. 0 for FER at week 5 **(Figure 3)**

Conclusions

- Post-hoc analyses of data from a Phase 3 clinical trial showed that mean serum phosphate decreased significantly in patients with IDA due to GI disorders following FCM, but not FER, starting as soon as 8 days following the first 750-mg dose, and did not return to baseline level by the end of the study period of 5 weeks
- This resulted in hypophosphatemia <2 mg/dL that remained unresolved in approximately one third of patients receiving FCM through the end of the 5-week study
- While this study was not designed to assess the occurrence of symptomatic hypophosphatemia, the persistence of severe hypophosphatemia among FCM patients at the end of the 5-week study period suggests the need for monitoring serum phosphate following FCM usage in clinical practice, especially if repeat dosing is a consideration

References

1. Cappellini MD,et al. etJournal of Internal Medicine, 2020, 287; 153–170. 2. Dignass AU, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. Journal of Crohn's and Colitis, 2015, 211–222 3. Zoller H et al. Curr Opin Nephrol Hypertens 2017, 26:266–275. 4. Wolf M et al. JCI Insight. 2018;3(23):e124486. 5. Glaspy J. et al. Therapeutics and Clinical Risk Management. 2020:16 245–259. 6. Imel EA, et al. Approach to the Hypophosphatemic Patient. J Clin Endocrinol Metab, March 2012, 97(3):696–706. 7. Adkinson NF, et al. Am J Hematol. 2018;93:683–690. 8. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. US Department of Health Human Services. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Disclosures

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Abbreviations:

IDA, iron deficiency anemia; gastrointestinal, GI; CKD, chronic kidney disease; Hgb, hemoglobin; FER, ferumoxytol; FCM, ferric carboxymaltose; CTCAE, Common Terminology Criteria for Adverse Events; GFR, glomerular filtration rate; ANCOVA, analysis of covariance; CI, confidence interval; OR, odds ratio

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