P51

Pooled analysis of the PHOSPHARE-IDA 04/05 studies: findings relevant to respiratory muscle function

Zoller H[1], Schaffalitzky de Muckadell P[2], Wolf M[3]

1. Medical University of Innsbruck, Innsbruck, Austria; 2. Pharmacosmos A/S, Holbæk, Denmark; 3. Duke University School of Medicine, Durham, North Carolina, USA

Introduction

Hypophosphatemia is associated with respiratory muscle weakness,[1-3] which is particularly relevant in the perioperative setting.

Ferric carboxymaltose (FCM) appears to be associated with higher rates of hypophosphatemia than iron isomaltoside 1000/ferric derisomaltose (IIM).[4,5]

The two identically designed, open-label, randomised controlled PHOSPHARE-IDA studies (IDA-04, IDA-05) compared the risks of hypophosphatemia in response to IIM versus FCM in patients with iron deficiency anaemia (IDA).

This analysis of pooled data from the PHOSPHARE-IDA studies assessed the efficacy of IIM and FCM in correcting IDA, compared the incidence of hypophosphatemia, and investigated the short-term effects of treatment on respiratory muscle strength/function.

Methods

Adults, >18 years, with IDA were randomised 1:1 to receive IIM (single infusion of 1,000 mg on Day 0) or FCM (FDA-approved dosing schedule: two infusions of 750 mg administered 1 week apart, i.e., first infusion on Day 0 and second infusion on Day 7).

Data were pooled to compare the effect of IIM and FCM on blood parameters: haemoglobin (Hb), ferritin, and transferrin saturation (TSAT).

The incidence of hypophosphatemia (phosphate <2.0 mg/dL [<0.65 mmol/L]) and of severe hypophosphatemia (phosphate ≤1.0 mg/dL [≤0.32 mmol/L]) were assessed.

Renal phosphate excretion, fibroblast growth factor 23 (FGF23), vitamin D, ionised calcium, and parathyroid hormone (PTH) were measured, as were markers of bone metabolism – alkaline phosphatase and bone-specific alkaline phosphatase.

Effects on skeletal muscle function (grip strength, arm lift and chair stand tests) and respiratory muscle function (maximal inspiratory pressure and maximal expiratory pressure) were also determined.

Grip strength, large proximal muscle strength, and respiratory muscle strength were tested on Days 0, 14 and 35.

Blood samples were collected (before iron administration, when relevant) at baseline (Day 0) and on Days 1, 7, 8, 14, 21, and 35. Other safety endpoints included the number of patients who experienced adverse events, including serious or severe hypersensitivity reactions.

Results

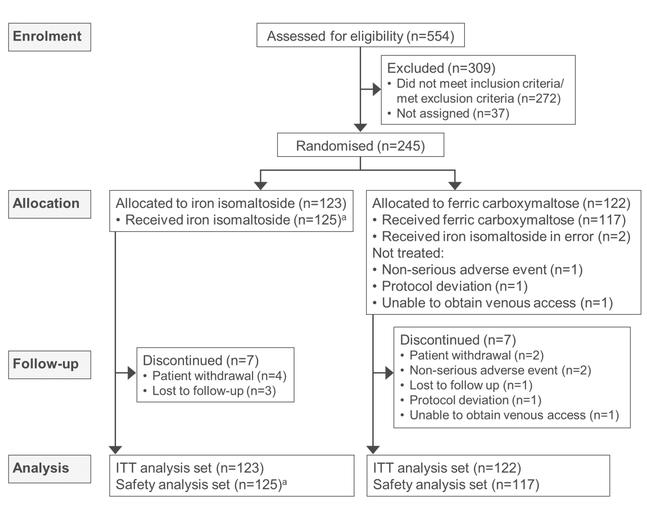
A total of 245 patients were randomised. Patient enrolment and flow through the study are shown in Figure 1.

A total of 125 patients received IIM (mean dose 1,008 mg) and 117 patients received FCM (mean dose 1,468 mg).

Although the aetiology of IDA was varied, the majority of patients were female and they had severe IDA due to gynaecological bleeding.

In each individual study, the two treatment groups were well balanced at baseline with respect to demographics and parameters of iron, phosphate, and calcium homeostasis.

Figure 1: Enrolment and randomisation of patients



[a]Two patients received IIM despite being randomised to FCM.

FCM=ferric carboxymaltose; IIM=iron isomaltoside; ITT=intention-to-treat

During the 35-day assessment period, Hb and ferritin rapidly normalised in both groups; TSAT initially peaked but was relatively unchanged by Day 35.

The incidence of hypophosphatemia (phosphate <2.0 mg/dL) was significantly higher in the FCM group versus the IIM group (74.4% versus 8.0%, p<0.0001; Figure 2).

Hypophosphatemia persisted at Day 35 in 43.0% of FCM-treated patients compared to 0.9% of IIM-treated patients (p<0.0001; Figure 2).

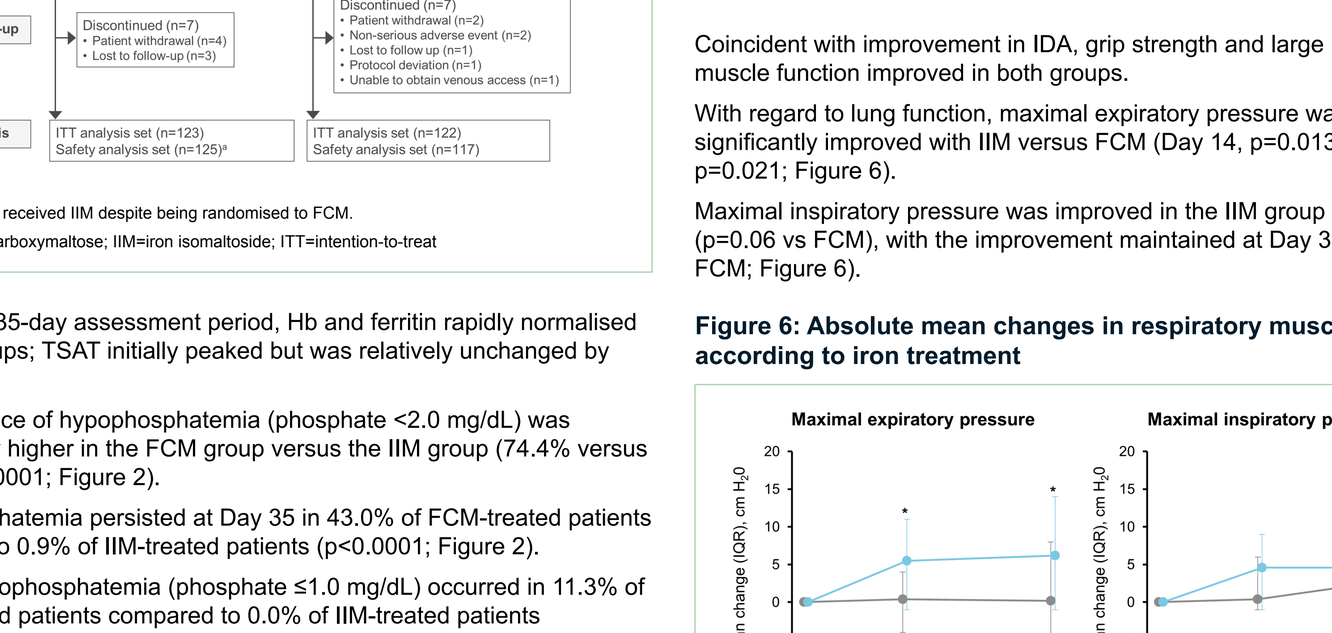
Severe hypophosphatemia (phosphate ≤1.0 mg/dL) occurred in 11.3% of FCM-treated patients compared to 0.0% of IIM-treated patients (p<0.0001).

FCM significantly increased intact FGF23 compared to IIM (p<0.0001; Figure 3).

Compared to treatment with IIM, FCM significantly: increased urinary fractional phosphate excretion (Figure 3); decreased serum 1,25-dihydroxyvitamin D (Figure 4); and increased PTH (Figure 4). These significant between-group differences persisted through to Day 35.

Compared to treatment with IIM, the FCM-induced decrease in ionised calcium was significant at Days 7, 8 and 21 (Figure 4).

Figure 2: Incidence of hypophosphatemia – serum phosphate <2.0 mg/dL

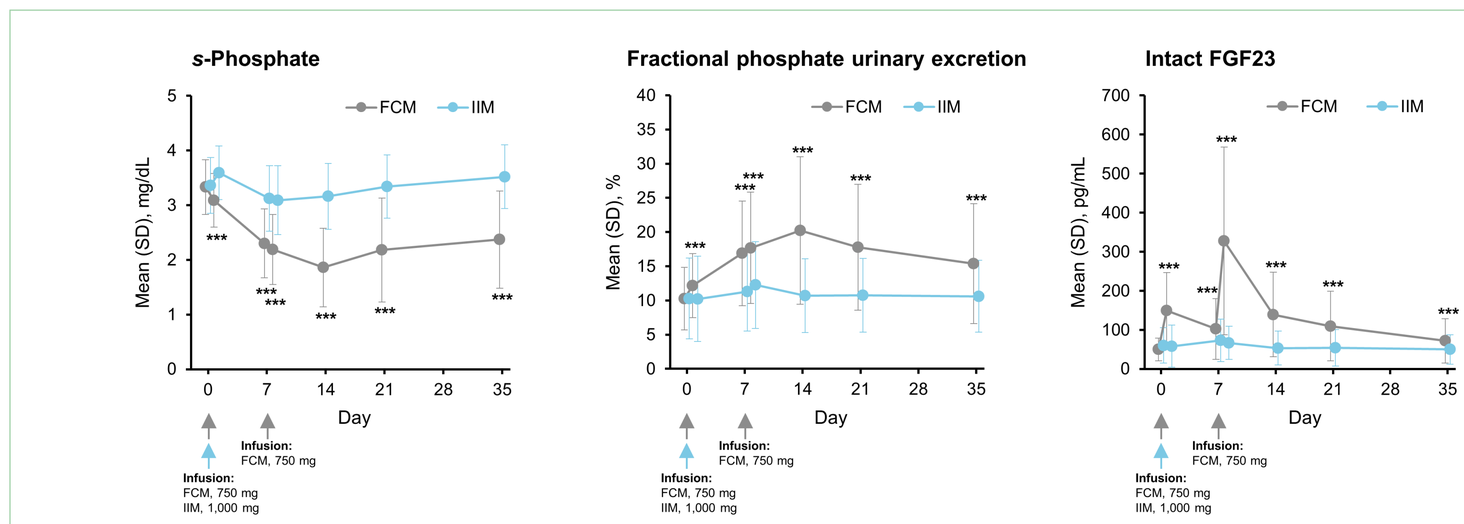


***p<0.001 between-group comparison; Cochran-Mantel-Haenszel

Values inside and above columns are n/N

[a]Serum phosphate ≤1.0 mg/dL occurred only in the ferric carboxymaltose group

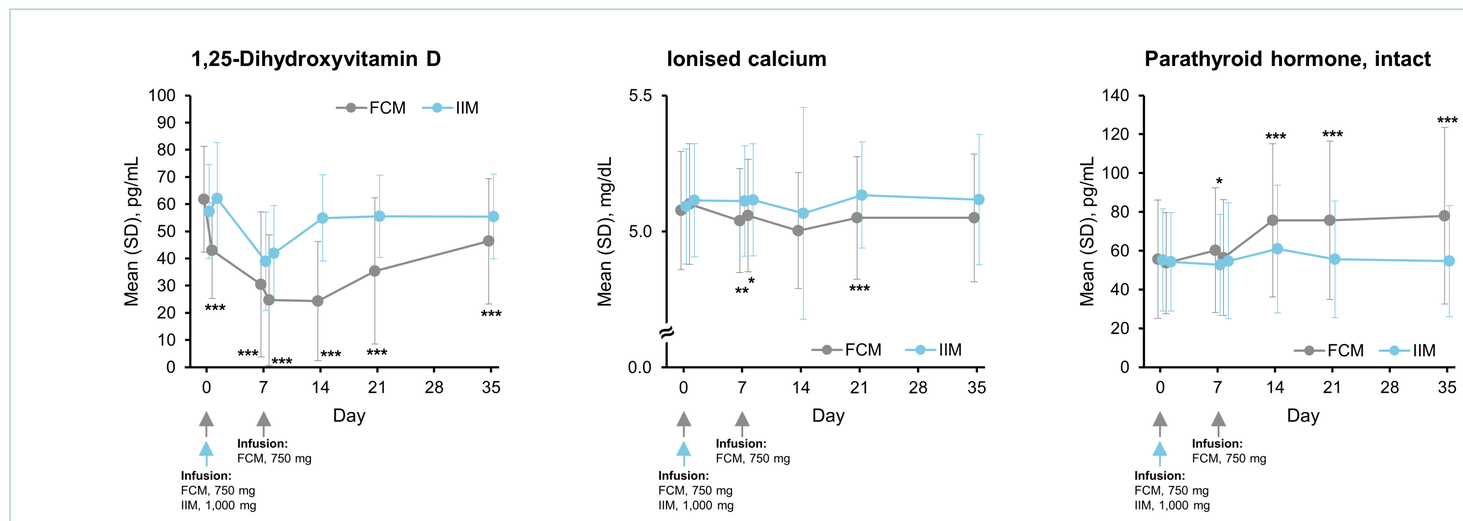
Figure 3: Changes in phosphate homeostasis according to iron treatment



***p<0.001 between-group comparison; MMRM

FCM=ferric carboxymaltose; IIM=iron isomaltoside; MMRM=mixed model for repeated measures; SD=standard deviation

Figure 4: Changes in parameters of calcium homeostasis according to iron treatment

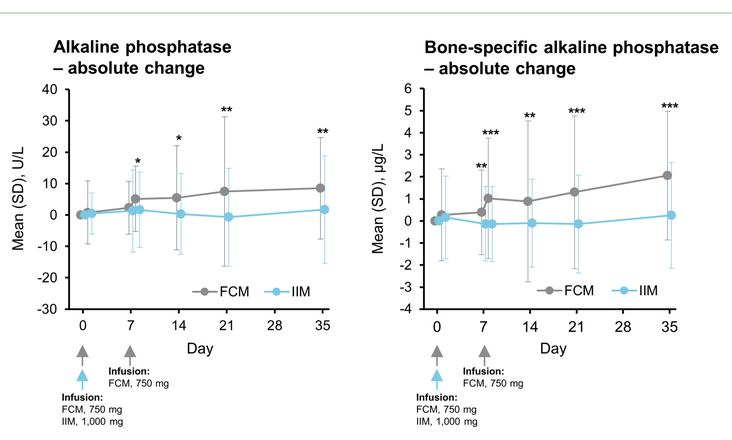


*p<0.05, **p<0.01, ***p<0.001 between-group comparison; MMRM

FCM=ferric carboxymaltose; IIM=iron isomaltoside; MMRM=mixed model for repeated measures; SD=standard deviation

These changes after FCM treatment were accompanied by significant increases in both total and bone-specific alkaline phosphatase that also persisted through to Day 35 (Figure 5).

Figure 5: Changes in markers of bone metabolism according to iron treatment



*p<0.05, **p≤0.01, ***p<0.001 between-group comparison; MMRM

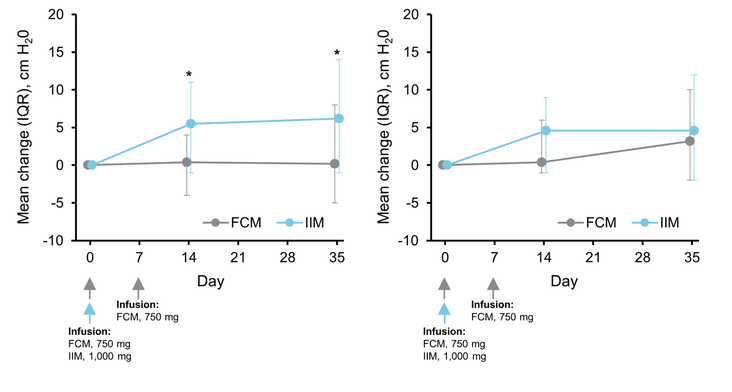
FCM=ferric carboxymaltose; IIM=iron isomaltoside; MMRM=mixed model for repeated measures; SD=standard deviation

Coincident with improvement in IDA, grip strength and large proximal muscle function improved in both groups.

With regard to lung function, maximal expiratory pressure was significantly improved with IIM versus FCM (Day 14, p=0.013; Day 35, p=0.021; Figure 6).

Maximal inspiratory pressure was improved in the IIM group at Day 14 (p=0.06 vs FCM), with the improvement maintained at Day 35 (p=0.68 vs FCM; Figure 6).

Figure 6: Absolute mean changes in respiratory muscle strength according to iron treatment



*p<0.05 between-group comparison; MMRM

FCM=ferric carboxymaltose; IIM=iron isomaltoside; IQR=interquartile range; MMRM=mixed model for repeated measures

A total of 113 adverse drug reactions were reported in 55 (47.0%) patients in the FCM group compared with 34 adverse drug reactions reported in 21 (16.8%) patients in the IIM group (p<0.0001).

Adverse drug reactions reported in ≥5% of patients are shown in Table 1.

Although 'hypophosphatemia' and 'blood phosphorus decreased' were the most commonly reported adverse drug reactions in the FCM group, reported in 38.5% of patients, the true incidence was 74.4% in this group according to the primary endpoint.

There were three serious or severe hypersensitivity reactions: one (swollen eyelid unilaterally) in the IIM group (0.8%), and two (swelling, and dyspnoea) in the FCM group (1.7%).

Table 1: Reported adverse drug reactions occurring at a frequency of ≥5% in either treatment group

Adverse drug reactions, n (%)	IIM (n=125)	FCM (n=117)
Any adverse drug reaction	21 (16.8)	55 (47.0)
Investigations		
Blood phosphorous decreased	0 (0.0)	19 (16.2)
Blood parathyroid hormone increased	4 (3.2)	6 (5.1)
Metabolism and nutrition disorders		
Hypophosphatemia	2 (1.6)	26 (22.2)
Gastrointestinal disorders		
Nausea	1 (0.8)	8 (6.8)

Data are presented for the safety analysis set

FCM=ferric carboxymaltose; IIM=iron isomaltoside

Conclusions

Treatment with IIM and FCM rapidly corrected IDA.

FCM caused hypophosphatemia in the majority of patients, initially due to acute increases in FGF23.

FCM, but not IIM, also induced FGF23-mediated changes in vitamin D and calcium homeostasis that triggered secondary hyperparathyroidism, which likely contributed to persistence of hypophosphatemia. These changes after FCM treatment were accompanied by significant increases in both total and bone-specific alkaline phosphatase that also persisted through to Day 35.

Consistent with case reports of pathological fractures following FCM use,[6-8] FCM induced significant elevations of biomarkers of bone turnover that are associated with osteomalacia.

Two weeks after treatment, when serum phosphate reached its nadir in the FCM group, patients' respiratory muscle strength was improved in the IIM group compared to the FCM group.

Rates of hypersensitivity reactions were low in both groups.

Blood managers administering iron preoperatively should be aware of hypophosphatemia as a complication of FCM that usually occurs within 1 to 4 weeks after iron administration, can persist for at least as long as 5 weeks, and can influence respiratory muscle function.

References

1. Amanzadeh J, Reilly RF Jr. Nat Clin Pract Nephrol 2006; 2 (3): 136–148.
2. Gravelyn TR, et al. Am J Med 1988; 84 (5): 870–876.
3. Zhao Y, et al. Biomed Rep 2016; 4 (4): 413–416.
4. Schaefer B, et al. PLoS One 2016; 11 (12): e0167146.
5. Zoller H, et al. Curr Opin Nephrol Hypertens 2017; 26 (4): 266–275.
6. Klein K, et al. BMJ Case Rep 2018. doi: 10.1136/bcr-2017-222851.
7. Urbina T, et al. J Bone Miner Res 2018; 33 (3): 540–542.
8. Schaefer B, et al. Gastroenterology 2017; 152 (6): e5–6.

Disclosures

Heinz Zoller has received honoraria for lecturing and consulting fees from Abbvie, BMS, Bayer, Gilead, MSD, Medice, Novartis, Pharmacosmos, and Vifor. Heinz Zoller has research grants from Abbvie, Gilead, and MSD.

Philip Schaffalitzky de Muckadell is an employee of Pharmacosmos A/S.

Myles Wolf has served as a consultant to Pharmacosmos A/S, and to Luitpold Pharmaceuticals.

Sponsorship

Supported by funding from Pharmacosmos A/S, Holbæk, Denmark.

Poster presented at the 20th Annual NATA Symposium, Berlin, 4–5 April 2019