Clinical Research Article

Risk Factors for and Effects of Persistent and Severe Hypophosphatemia Following Ferric Carboxymaltose

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Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D (active vitamin D); 24,25(OH)2D, 24,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; cFGF23, C-terminal fibroblast growth factor 23; CTx, C-terminal telopeptide; FCM, ferric carboxymaltose; FDI, ferric derisomaltose; FGF23, fibroblast growth factor 23; iFGF23, intact fibroblast growth factor 23; LS, least squares; OR, odds ratio; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone.

Abstract

Context: Hypophosphatemia, osteomalacia, and fractures are complications of certain intravenous iron formulations.

Objective: This study investigated risk factors for incident, severe, and persistent hypophosphatemia, and associated alterations in bone and mineral biomarkers following intravenous iron treatment.

Methods: We analyzed data from the PHOSPHARE-IDA randomized clinical trials, comprising 245 patients aged 18 years or older with iron deficiency anemia at 30 outpatient clinics in the United States who received intravenous ferric carboxymaltose (FCM) or ferric derisomaltose (FDI). Outcome measures included serum phosphate, intact fibroblast growth factor-23 (iFGF23), 1,25-dihydroxyvitamin D (1,25(OH)2D), 25-hydroxyvitamin D; cFGF23, C-terminal fibroblast growth factor 23; CTx, C-terminal telopeptide; FCM, ferric carboxymaltose; FDI, ferric derisomaltose; FGF23, fibroblast growth factor 23; iFGF23, intact fibroblast growth factor 23; LS, least squares; OR, odds ratio; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone.

Results: FCM was the only consistent risk factor for incident hypophosphatemia (< 2.0 mg/dL; odds ratio vs FDI: 38.37; 95% CI: 16.62, 88.56; P < 0.001). Only FCM-treated patients developed severe hypophosphatemia (< 1.0 mg/dL; 11.3%; 13/115) or persistent hypophosphatemia (< 2.0 mg/dL at study end; 40.0%; 46/115). More severe hypophosphatemia associated with significantly greater increases in iFGF23, PTH, and alkaline phosphatase, and more severe decreases in 1,25(OH)2D and ionized calcium (all P < 0.05). Patients with persistent vs resolved hypophosphatemia demonstrated significantly greater changes in iFGF23, PTH, 1,25(OH)2D, and N-terminal procollagen-1 peptide levels (all P < 0.01), but alkaline phosphatase increased similarly in both groups.
Conclusion: Treatment with FCM was the only consistent risk factor for hypophosphatemia. Patients who developed severe or persistent hypophosphatemia after FCM treatment manifested more severe derangements in bone and mineral metabolism. Changes in bone biomarkers continued beyond resolution of hypophosphatemia, suggesting ongoing effects on bone that may help explain the association of FCM with osteomalacia and fractures.

Key Words: hypophosphatemia, FGF23, intravenous iron, alkaline phosphatase, PTH, clinical trials

Ferric carboxymaltose (FCM; Injectafer in the United States, American Regent, Inc.; Ferinject in the European Union, Vifor Pharma; commercially available in the United States since 2013) and ferric derisomaltose (FDI; formerly known as iron isomaltoside; Monofer in the United States; Monoferric in the European Union, Pharmacosmos A/S; commercially available in the United States since 2020) are iron preparations that are available for intravenous use to rapidly correct iron deficiency (1-5). Both preparations increase hemoglobin comparably and with minimal risk of hypersensitivity reactions (3, 4, 6-10). FCM and FDI can decrease serum phosphate concentrations by increasing renal phosphate excretion, but the incidence of hypophosphatemia is significantly higher after FCM vs FDI treatment (11, 12). In addition, FCM but not FDI has been shown to cause severe hypophosphatemia (serum phosphate ≤ 1.0 mg/dL) and hypophosphatemia that can persist beyond 5 weeks after its initial administration (11-13).

Hypophosphatemia after FCM is mediated by increases in the phosphate-regulating hormone fibroblast growth factor-23 (FGF23) (14). High levels of biologically active, intact FGF23 (iFGF23) increase urinary phosphate excretion and suppress 1,25-dihydroxyvitamin D (1,25(OH)2D) concentrations by reducing the activation of 25-hydroxyvitamin D (25(OH)D) and accelerating the degradation of 1,25(OH)2D (15). The resultant reduction in serum calcium causes secondary hyperparathyroidism that maintains renal phosphate wasting via the phosphaturic effects of parathyroid hormone (PTH) (15). These biochemical changes were recently summarized as “6H-syndrome” (hypophosphatemia, high FGF23, high urinary phosphate excretion, hypocalcitriolemia, hypocalcemia, and secondary hyperparathyroidism) (16).

In the PHOSPHARE-IDA trials, which were a pair of identically designed, randomized clinical trials, PHOSPHARE IDA-04 and PHOSPHARE IDA-05 (ClinicalTrials.gov, NCT03238911 and NCT03237065), for which the primary results were previously published (12). In brief, 245 patients aged 18 years or older with iron deficiency anemia (hemoglobin ≤ 11 g/dL and ferritin < 100 ng/mL), intolerance or unresponsiveness to oral iron, normal serum phosphate, and normal kidney function were recruited from 30 outpatient clinic sites in the United States between October 2017 and June 2018 (12). Patients were randomized (1:1) to either 2 doses of FCM (750 mg on day 0 and on day 7), or a single infusion of FDI (1000 mg on day 0), in accord with their FDA-approved labeling (12, 17, 18). The primary outcome was incident hypophosphatemia, defined as serum phosphate < 2.0 mg/dL at any time from baseline to day 35 (12). In addition to hematological markers, serum phosphate, urinary phosphate excretion, ionized calcium, iFGF23, and C-terminal FGF23 (cFGF23), vitamin D metabolites [25(OH)D, 1,25(OH)2D, and 24,25-dihydroxyvitamin D (24,25(OH)2D)], bone biomarkers (N-terminal procollagen-1 peptide [PINP], C-terminal telopeptide [CTx], alkaline phosphatase [total and bone-specific]), and PTH were measured on days 0, 1, 7, 8, 14, 21, and 35 (12). The trials were approved by a single institutional review board (Western Institutional
Review Board, Puyallup, Washington; 98374-2115) and all patients provided written informed consent (12).

For the current study, we analyzed the pooled cohort of 242 patients who received at least 1 dose of trial drug (Fig. 1); the 3 randomized patients who were not treated were excluded. For analyses of incident hypophosphatemia, patients with no post-baseline phosphate measurements \( (n = 3) \) were imputed as hypophosphatemic (as in the trials’ primary analysis (12)). For analyses grouped by severity of hypophosphatemia, patients were categorized as: no hypophosphatemia (serum phosphate \( \geq 2.0 \) mg/dL at all visits), moderate hypophosphatemia (serum phosphate \( > 1.0 \) to \( < 2.0 \) mg/dL at any post-baseline visit), or severe hypophosphatemia (serum phosphate \( \leq 1.0 \) mg/dL at any post-baseline visit; Fig. 1). For analyses grouped by duration of hypophosphatemia, patients were considered to have persistent hypophosphatemia if they developed incident hypophosphatemia between days 1 and 14 and remained hypophosphatemic (serum phosphate \( < 2.0 \) mg/dL) on day 35; patients were considered to have recovered if they developed hypophosphatemia between day 1 and day 14, but their serum phosphate was \( \geq 2.0 \) mg/dL on day 35 (Fig. 1). Patients with no post-baseline phosphate measurement were excluded from the analyses grouped by severity and duration of hypophosphatemia. Nine patients first developed hypophosphatemia on day 21 or day 35 (Fig. 1). These patients could not be classified as persistent or recovered based on our definitions and were excluded from the analyses of duration of hypophosphatemia.

**Statistical Analysis**

We used SAS (version 9.4, Cary, NC) to perform all analyses. Baseline characteristics and demographics are presented as frequencies and percentages, or as means and standard deviations.

We investigated baseline risk factors for incident, severe, and persistent hypophosphatemia using univariate and multivariate logistic regression. Candidate risk factors included age, sex, race (White, African American, Asian, or other), ethnicity (Hispanic or Latino, or non-Hispanic or non-Latino), patient weight, cause of iron deficiency anemia (gynecological or other causes), hematological parameters (hemoglobin, ferritin, transferrin, and transferrin

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**Figure 1.** Patient flow according to study drug, hypophosphatemia severity, and hypophosphatemia duration. Abbreviations: FCM, ferric carboxymaltose; FDI, ferric derisomaltose. *For patients with no post-baseline measurements, serum phosphate level was imputed as < 2.0 mg/dL (as in the primary clinical trial analysis). †Patients with no post-baseline serum phosphate measurements. ‡Patients who could not be categorized according to the definitions of “recovered” and “persistent,” due to low phosphate only on day 21 and/or day 35.
In contrast, 74.4% (87/117) of FCM-treated patients developed hypophosphatemia, which was severe in 11.3% (13/115) of patients (12). In the current analysis, no FDI-treated patients developed persistent hypophosphatemia. Of all FCM-treated patients, 40.0% (46/115) had persistent hypophosphatemia on day 35, including 12 of the 13 who developed severe hypophosphatemia (Fig. 1).

Baseline Risk Factors for Hypophosphatemia

Treatment with FCM was the strongest risk factor for incident hypophosphatemia (odds ratio [OR] vs FDI: 38.37; 95% CI: 16.62, 88.56; Table 2). Higher baseline PTH and lower body weight were also associated with increased risk of incident hypophosphatemia (Table 2). Since we defined incident hypophosphatemia using a fixed threshold that does not consider the baseline serum phosphate, we also analyzed baseline predictors of change in serum phosphate on a continuous scale after iron treatment. FCM vs FDI treatment was associated with the largest magnitude decrease in serum phosphate from baseline (−1.08 mg/dL; 95% CI: −1.22, −0.94; Table 2). Higher baseline serum phosphate and lower ferritin concentration were also associated with larger magnitude decreases in serum phosphate from baseline (Table 2). Unlike the analysis of incident hypophosphatemia, baseline PTH was not associated with the magnitude decrease in serum phosphate.

In analyses of baseline risk factors for severe hypophosphatemia and persistent hypophosphatemia, only FCM-treated patients could be investigated because no FDI-treated patient developed severe or persistent hypophosphatemia (Fig. 1). Among FCM-treated patients, only lower baseline PTH was associated with the development of severe hypophosphatemia (Table 2). Lower baseline ferritin and lower baseline serum phosphate were the only independent baseline risk factors for persistent hypophosphatemia (Table 2).

Hyponphosphatemia Severity

The primary manuscript reported results for the entire FCM and FDI groups (12), which may underestimate the magnitude of effects on bone and mineral parameters among patients who developed hypophosphatemia by mixing their data with data from those who did not develop hypophosphatemia. In longitudinal analyses according to the severity of hypophosphatemia (Fig. 2), more severe hypophosphatemia was associated with more severe derangements in iFGF23, ionized calcium, 1,25(OH)2D, PTH, alkaline phosphatase, and P1NP. Among patients with severe hypophosphatemia, the maximal LS mean increase in iFGF23 was 456 pg/mL (95% CI: 340, 571) on day 8 and the maximal LS

Results

Baseline demographic, hematological, and biochemical characteristics of the study population are summarized in Table 1. As detailed in the primary report, the incidence of hypophosphatemia was 8.0% (10/125) in FDI-treated patients, none of whom developed severe hypophosphatemia (12). In contrast, 74.4% (87/117) of FCM-treated patients
mean reduction from baseline in serum phosphate was 2.20 mg/dL (95% CI: 1.92, 2.48) on day 14. PTH was significantly higher and 1,25(OH)\(_2\)D was significantly lower in the severe vs the moderate hypophosphatemia group from day 21 onwards. Ionized calcium was significantly lower in the severe vs the moderate hypophosphatemia group from day 8 onwards. Alkaline phosphatase increased to significantly higher values in the severe vs the moderate hypophosphatemia group on day 14 and day 35.

**Hypophosphatemia Duration**

Comparisons of bone and mineral metabolism among FCM-treated patients who developed incident hypophosphatemia and either recovered (n = 32) or...
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experienced persistent hypophosphatemia (n = 46) at day 35 are presented in Fig. 3; FCM-treated patients who did not develop hypophosphatemia are shown for comparison and completeness. Beginning on day 8 and throughout the remainder of follow-up, iFGF23 was significantly higher among those who remained persistently hypophosphatemic compared with those who recovered. In accordance with the known biological effects of FGF23, 1,25(OH)2D decreased significantly more by day 1 and remained significantly lower at all subsequent visits in the persistent hypophosphatemia vs the recovered group. Compared with the recovered group, PTH was significantly higher on day 35 and P1NP was significantly lower on day 21 and day 35 in the persistent hypophosphatemia group. Changes in CTx did not differ between groups. Although alkaline phosphatase increased from baseline in both the persistent and recovered hypophosphatemia groups, there was no difference between these groups at day 35.

Postinfusion Risk Factors for Persistent Hypophosphatemia

In the United States, FCM is administered in 2 doses of 750 mg each, 1 week apart (17). Before administering the second FCM dose, clinicians have the opportunity to assess the effects of the first dose on mineral metabolism, which can be used to determine whether to give the second dose. Among the biochemical parameters, lower 1,25(OH)2D and higher iFGF23 concentrations on day 14 were independent predictors for development of persistent hypophosphatemia (Table 3). It is also important for clinicians to identify which patients with FCM-induced hypophosphatemia will require the closest follow-up for persistent hypophosphatemia, since rates of persistent hypophosphatemia were highest on day 14. Lower 1,25(OH)2D and lower serum phosphate concentrations on day 7 were also independent predictors for development of persistent hypophosphatemia.

Table 2. Baseline predictors for development of incident, persistent and severe hypophosphatemia, and for magnitude of change in serum phosphate from baseline to nadir

| Hypophosphatemia | Change in serum phosphate |
|------------------|--------------------------|
| Incident (n = 238) | Persistent (n = 106)* | Severe (n = 114)* | From baseline to nadir (n = 225) |
| Dependent variable | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | p | β-coefficient of change (95% CI) | P |
| Weight, per 5 kg increase | 0.88 (0.80; 0.97) | 0.013 | - | - | - | - | - | - |
| Phosphate, per 0.5 mg/dL increase | - | - | 0.63 (0.40; 1.00) | 0.048 | - | - | - | - |
| PTH, per 10 pg/mL increase | 1.23 (1.06; 1.42) | 0.006 | - | - | 0.74 (0.55; 1.00) | 0.047 | - | - |
| Ferritin, per 10 ng/mL increase | - | - | 0.59 (0.35; 0.99) | 0.046 | - | - | - | - |
| Treatment, FCM vs FDI | 38.37 (16.62; 88.56) | <0.001 | - | - | - | - | - | - |

Results are from the final parsimonious multivariate models that originally considered the following candidate factors: age, sex, race (White, African American, Asian, or other), ethnicity (Hispanic or Latino, or non-Hispanic or non-Latino), patient weight, cause of iron deficiency anemia (gynecological or other causes), hematological parameters (hemoglobin, ferritin, transferrin, and transferrin saturation), bone and mineral metabolism markers (serum phosphate, cFGF23, iFGF23, ionized calcium, PTH, 25(OH)D, 1,25(OH)2D, total alkaline phosphatase), and randomized drug assignment (FCM or FDI). Incident hypophosphatemia: serum phosphate < 2.0 mg/dL at any time; persistent hypophosphatemia: serum phosphate < 2.0 mg/dL at any time on days 1–14 that was not resolved on day 35; severe hypophosphatemia: serum phosphate ≤ 1.0 mg/dL at any time. Only significant predictors from the final parsimonious models are shown.

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; cFGF23, C-terminal fibroblast growth factor-23; FCM, ferric carboxymaltose; FDI, ferric dextramaltose; iFGF23, intact fibroblast growth factor-23; OR, odds ratio; PTH, parathyroid hormone.

*Baseline predictors of persistent hypophosphatemia and severe hypophosphatemia were assessed only in the FCM-treated patients as neither persistent nor severe hypophosphatemia occurred after FDI treatment.
Figure 2. LS mean change (95% CI) in biochemical parameters from baseline to day 35 in patients grouped by hypophosphatemia severity (FCM-treated patients only). *P < 0.05, **P < 0.01, ***P < 0.001 for comparisons of severe vs moderate hypophosphatemia; to limit multiple testing, comparisons vs no hypophosphatemia were omitted. Severe hypophosphatemia: serum phosphate ≤ 1.0 mg/dL at any time from baseline to day 35; moderate hypophosphatemia: serum phosphate > 1.0 to < 2.0 mg/dL at any time from baseline to day 35; no hypophosphatemia: serum phosphate ≥2.0 mg/dL at all times. Data are presented for FCM-treated patients only as no FDI-treated patients developed severe hypophosphatemia.

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; CTx, C-terminal telopeptide; FCM, ferric carboxymaltose; iFGF23, intact fibroblast growth factor-23; iPTH, intact parathyroid hormone; P1NP, N-terminal procollagen-1 peptide.
Figure 3. LS mean change (95% CI) in biochemical parameters from baseline to day 35 grouped by hypophosphatemia duration (FCM-treated patients only). *P < 0.05, **P < 0.01, ***P < 0.001 for comparisons of persistent vs recovered hypophosphatemia; to limit multiple testing, comparisons vs no hypophosphatemia were omitted. Persistent hypophosphatemia: serum phosphate < 2.0 mg/dL at any time on days 1–14 that was not resolved on day 35. Recovered hypophosphatemia: serum phosphate < 2.0 mg/dL at any time on days 1–14 that resolved by day 35; no hypophosphatemia: serum phosphate ≥ 2.0 mg/dL at all times. Data are presented for FCM-treated patients only as no FDI-treated patients developed persistent hypophosphatemia. Abbreviations: 1,25(OH)₂D, 1,25-dihydroxyvitamin D; CTx, C-terminal telopeptide; FCM, ferric carboxymaltose; iFGF23, intact fibroblast growth factor-23; iPTH, intact parathyroid hormone; P1NP, N-terminal procollagen-1 peptide.
treatment was the most potent and the only consistent risk factor for development of incident hypophosphatemia and for the magnitude of change in serum phosphate from baseline to its post–iron infusion nadir. Differences in patient weight and baseline serum phosphate, ferritin, and PTH were among the few other risk factors that were identified for incident, severe, or persistent hypophosphatemia, but their effects were of modest magnitude and were inconsistent across the analyses (Table 2). These results are broadly concordant with those from the FIRM trial that compared FCM with ferumoxytol, and also found that FCM use was the strongest risk factor for development of incident and persistent hypophosphatemia (19). In aggregate, these results demonstrate that there are few characteristics beyond FCM use that can inform clinicians which patients are at higher risk of developing hypophosphatemia after receiving intravenous iron.

Longitudinal analyses demonstrated that serum phosphate decreased by 2.20 mg/dL from baseline among patients who were treated with FCM and developed severe hypophosphatemia. By comparison, a decrease of 1.46 mg/dL was reported in the overall FCM group (12). Thus, the current analysis demonstrates that the severity of hypophosphatemia in the most affected patients can be underestimated when considering mean changes in an overall population that also includes unaffected patients. The longitudinal analyses stratified by hypophosphatemia severity also exposed the true magnitude of the derangements in markers of mineral metabolism among FCM-treated patients who developed moderate or severe hypophosphatemia compared to the overall FCM group. In support of the underlying mechanism of FCM-induced hypophosphatemia, these analyses show that worsening severity of hypophosphatemia is associated with more marked elevation of iFGF23, lower 1,25(OH)2D, and more pronounced hypocalcemia and secondary hyperparathyroidism.

More severe and more prolonged hypophosphatemia after FCM treatment were also associated with changes in bone biomarkers, including increased alkaline phosphatase and decreased P1NP, but little change in CTx. The divergence of the P1NP and CTx responses suggests uncoupling of normal bone remodeling in a pattern that is reminiscent of the effect of corticosteroids, which are known to cause bone loss and increase the risk of fracture (20). The elevated alkaline phosphatase is a typical finding in osteomalacia (21), and numerous case reports describe elevated alkaline phosphatase in the setting of osteomalacia and fractures after FCM treatment (22). However, in the absence of bone histology or sophisticated bone imaging, we can only speculate why the bone formation markers P1NP and alkaline phosphatase diverged. It is possible that the pattern of bone biomarkers differs when well-established osteomalacia comes to clinical attention after a longer and highly variable duration of bone disease than the current situation in which we studied patients soon after the onset of bone injury, the exact timing of which was known. Alternatively, the mechanism of bone disease due to FCM might differ from other causes of osteomalacia and produce a different pattern of bone biomarkers. While further research is needed to investigate the mechanisms of bone disease after FCM and the associated evolution of changes in bone biomarkers over time, it is noteworthy that elevated alkaline phosphatase and reduced P1NP persisted through the end of the study period in patients who developed FCM-induced hypophosphatemia regardless of its duration. This suggests that bone injury can occur after a single course of FCM and can continue even after serum phosphate returns to normal, as has been previously reported (23). As a corollary, resolution of hypophosphatemia after FCM treatment does not necessarily signify normalization of bone and mineral metabolism. Thus, the current data support recent updates to the product label for FCM in the United States, to include a warning on symptomatic hypophosphatemia, and in the European Union and in Brazil, to inform prescribers that FCM-induced hypophosphatemia can cause osteomalacia and fractures (17, 24, 25). They also support the need for long-term studies of bone health in patients with a history of FCM-induced hypophosphatemia of any duration.

The updated regulatory labeling for FCM also includes recommendations to monitor serum phosphate levels (17, 24). However, the optimal timing for when to monitor phosphate and whether additional biomarkers might also be relevant is not known. Given the FDA-approved administration schedule for FCM is 2 doses of 750 mg, 1 week apart (17), clinicians have a window to assess whether or not to administer the second dose. The results presented in this study could help guide the risk assessment of FCM treatment. We identified lower serum phosphate and 1,25(OH)2D on day 7 as independent predictors of persistent hypophosphatemia at day 35. Since the availability of testing for 1,25(OH)2D is inconsistent and the turnaround time can be long, we propose that all patients who receive FCM should have their serum phosphate tested at baseline and on day 7 to determine whether or not to administer the second dose. The results presented in this study could help guide the risk assessment of FCM treatment (Table 3). Among patients who receive the second FCM dose, measuring their 1,25(OH)2D and iFGF23 levels 1 week later might also help clinicians identify which patients require the closest follow-up for persistent hypophosphatemia. Alternatively, using an iron
formulation with low hypophosphatemia risk may help avoid downstream consequences of hypophosphatemia altogether.

Strengths of this study include the randomized design and the detailed biochemical characterization of patients at multiple time points. Limitations include the post hoc nature of this analysis, the use of different iron doses between the 2 treatment arms, and the preponderance of female participants that could limit generalizability to men. The relatively short duration of the trials precluded a determination of how long beyond day 35 hypophosphatemia and associated changes in bone and mineral metabolism persisted. While prior studies reported that hypophosphatemia persisted after a single course of FCM for 3 to 9 months in some patients (13, 26-28), there are limited data on the long-term effects of FCM-induced hypophosphatemia on bone. Another limitation of the short duration of follow-up is that we could not assess effects on clinical outcomes, such as fractures, that have been reported in multiple case reports of patients after treatment with FCM (29-31). Additional studies with long-term clinical surveillance are needed to assess the skeletal safety of FCM.

In conclusion, hypophosphatemia can occur after both FDI and FCM, but the incidence was higher after FCM, and severe and persistent hypophosphatemia was observed only after FCM treatment. Compared with moderate and recovered hypophosphatemia, severe and persistent hypophosphatemia were associated with greater and more prolonged elevations of iFGF23, greater reductions in 1,25(OH)2D, and more severe secondary hyperparathyroidism. These changes were associated with changes in biomarkers suggesting impaired bone metabolism that highlight the importance of preventing hypophosphatemia because its clinical consequences could extend beyond the duration of hypophosphatemia.

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Dr. Schaefer reported receiving personal fees from Pharmacosmos A/S, and Vifor Pharma, and grants and personal fees from AbbVie, and Gilead outside the submitted work. Dr. Zoller reported receiving grants, personal fees, and nonfinancial support from AbbVie, Gilead, Pharmacosmos A/S, and Vifor Pharma; personal fees from Merck; personal fees and nonfinancial support from Bayer; grants from Merck Sharp & Dohme; and honoraria for lecturing from Bristol-Myers Squibb, Medice, Merz, and Novartis outside the submitted work. Dr. Wolf reported receiving personal fees from Akebia, Ardelyx, AstraZeneca, Bayer, Jnana, Pharmacosmos A/S, Unicycive, and Walden Biosciences outside the submitted work.

Additional Information

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References

1. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832-1843.
2. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet. 2021;397(10270):233-248.
3. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. Transfusion. 2014;54(2):306-315.
4. Stein J, Walper A, Klemm W, Farrag K, Aksan A, Dignass A. Safety and efficacy of intravenous iron isomaltoside for correction of anemia in patients with inflammatory bowel disease in everyday clinical practice. Scand J Gastroenterol. 2018;53(9):1059-1065.
5. Blumenstein I, Shanbhag S, Langguth P, Kalra PA, Zoller H, Lim W. Newer formulations of intravenous iron: a review of their chemistry and key safety aspects - hypersensitivity, hypophosphatemia, and cardiovascular safety. Expert Opin Drug Saf. 2021;20(7):757-769.
6. Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrol Dial Transplant*. 2021;36(1):111-120.

7. Pollock RF, Muduma G. A systematic literature review and indirect comparison of iron isomaltoside and ferric carboxymaltose in iron deficiency anemia after failure or intolerance of oral iron treatment. *Expert Rev Hematol*. 2019;12(2):129-136.

8. Auerbach M, Henry D, Derman RJ, Achebe MM, Thomsen LL, Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. *Am J Hematol*. 2019;94(9):1007-1014.

9. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. *Am J Hematol*. 2017;92(3):286-291.

10. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. *Nephrol Dial Transplant*. 2014;29(4):833-842.

11. Schaefer B, Tobiasch M, Viveiros A, et al. Hypophosphatemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside-a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2020;87(5):2256-2273.

12. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. *JAMA*. 2020;323(5):432-443.

13. Detlie TE, Lindstrom JC, Jahnsen ME, et al. Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside. *Aliment Pharmacol Ther*. 2019;50(4):397-406.

14. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res*. 2013;28(8):1793-1803.

15. Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat Rev Nephrol*. 2020;16(1):7-19.

16. Schaefer B, Meindl E, Wagner S, Tilg H, Zoller H. Intravenous iron supplementation therapy. *Mol Aspects Med*. 2020;75:100862.

17. Injectafer® (ferric carboxymaltose). *Prescribing Information*. Vifor International, Inc.; 2020.

18. Monoferic® (ferric derisomaltose). *Prescribing Information*. Pharmacosmos A/S; 2020.

19. Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight*. 2018;3(23):e124486.

20. Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. *Nat Rev Endocrinol*. 2020;16(8):437-447.

21. Peach H, Compston JE, Vedi S, Horton IW. Value of plasma calcium, phosphate, and alkaline phosphatase measurements in the diagnosis of histological osteomalacia. *J Clin Pathol*. 1982;35(6):625-630.

22. Schaefer B, Tobiasch M, Wagner S, et al. Hypophosphatemia after intravenous iron therapy: comprehensive review of clinical findings and recommendations for management. *Bone*. 2021;154:116202.

23. Klein K, Asaad S, Econs M, Rubin JE. Severe FGF23-based hypophosphataemic osteomalacia due to ferric carboxymaltose administration. *BMJ Case Rep*. 2018;2018:bcr2017222851.

24. Ferinject® (ferric carboxymaltose). *Summary of Product Characteristics*. Vifor France; 2020.

25. Ferinject® (ferric carboxymaltose). *Prescribing Information (Brazil)*. Vifor (International) Inc.; 2020.

26. Frazier R, Hodakowski A, Cai X, et al. Effects of ferric carboxymaltose on markers of mineral and bone metabolism: A single-center prospective observational study of women with iron deficiency. *Bone*. 2020;141:115559.

27. Schaefer B, Württinger P, Finkenstedt A, et al. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. *PLoS One*. 2016;11(12):e0167146.

28. Rosano G, Schiefeke I, Göhring U-M, Fabien V, Bonassi S, Stein J. A pooled analysis of serum phosphate measurements and potential hypophosphataemia events in 45 interventional trials with ferric carboxymaltose. *J Clin Med*. 2020;9(11):3587.

29. Zoller H, Schaefer B, Gladny B. Iron-induced hypophosphatemia: an emerging complication. *Curr Opin Nephrol Hypertens*. 2017;26(4):266-275.

30. Sangrós Sahún MJ, Goñi Gironés E, Camarero Salazar A, Estébanez Estébanez C, Lozano Martínez ME. Symptomatic hypophosphataemic osteomalacia secondary to the treatment with iron carboxymaltose detected in bone scintigraphy. *Rev Esp Med Nucl Imagen Mol*. 2016;35(6):391-393.

31. Schaefer B, Gladny B, Zoller H. Blood and bone loser. *Gastroenterology*. 2017;152(6):e5-e6.