Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with ferric carboxymaltose or iron isomaltoside

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Summary
Background: Iron deficiency and iron deficiency anaemia are common complications in inflammatory bowel disease (IBD). In patients with moderate-to-severe anaemia, oral iron intolerance or ineffectiveness of oral iron, ferric carboxymaltose and iron isomaltoside are widely used. Hypophosphatemia is a side effect of both preparations.
Aims: To investigate the occurrence of hypophosphatemia in IBD patients with iron deficiency/iron deficiency anaemia treated with high-dose intravenous iron.
Methods: A prospective observational study of adult IBD patients with iron deficiency/iron deficiency anaemia was conducted at two study sites where patients received 1000 mg of ferric carboxymaltose or iron isomaltoside. At baseline, weeks 2 and 6, blood and faecal samples were collected. The primary endpoint was to determine the incidence of moderate-to-severe hypophosphatemia. Secondary endpoints included the total incidence of hypophosphatemia, possible risk factors for hypophosphatemia, and response to single-dose intravenous iron.
Results: One hundred and thirty patients were included. In the per-protocol set, 52 patients received ferric carboxymaltose and 54 patients received iron isomaltoside. Ferric carboxymaltose treatment had a significantly higher incidence of moderate-to-severe hypophosphatemia compared with iron isomaltoside at week 2 (56.9% vs 5.7%, P < 0.001) and a higher incidence at week 6 (13.7% vs 1.9%, P = 0.054). The overall incidence of hypophosphatemia was significantly higher with ferric carboxymaltose compared with iron isomaltoside treatment at weeks 2 (72.5% vs 11.3%, P < 0.001) and 6 (21.6% vs 3.7%, P = 0.013).
Conclusions: In IBD patients with iron deficiency/iron deficiency anaemia, ferric carboxymaltose was associated with higher incidence, severity and persistence of hypophosphatemia compared with iron isomaltoside. The presence of moderate-to-severe hypophosphatemia beyond 6 weeks is a clinical concern that requires further investigation.

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A common complication of inflammatory bowel disease (IBD) is anaemia, which in adults with IBD, prevalence is approximately 60% at the time of diagnosis and approximately 30%-40% at any other time. Iron deficiency has been identified as a major cause of anaemia. Typical symptoms of iron deficiency anaemia include fatigue, headache, dyspnoea, vertigo, and tachycardia, but iron deficiency anaemia can also manifest as restless legs syndrome, and reduced cognitive and physical performance. Iron deficiency anaemia, therefore, negatively impacts the quality of life of patients with IBD.

Iron deficiency and iron deficiency anaemia should be treated with iron supplementation. The European Crohn’s and Colitis Organisation (ECCO) guidelines recommend high-dose intravenous iron over oral supplementation because intravenous iron is more effective, delivers a faster response, and is better tolerated. However, iron deficiency and iron deficiency anaemia have been found to recur after therapy with intravenous iron in IBD patients (median 19 months for iron deficiency and 10 months for iron deficiency anaemia), indicating a need for repeated infusions.

Ferric carboxymaltose (Ferinject®; Vifor Pharma Ltd) and iron isomaltoside (Monofer®; Pharmacosmos A/S) are the most widely used high-dose intravenous iron preparations in Europe. Hypophosphatemia is a recognised but not well-known side effect of both intravenous iron preparations. There are numerous published case reports that document the risk of hypophosphatemia associated with ferric carboxymaltose treatment with potential severe complications. Data from iron isomaltoside clinical trials suggest lower rates of hypophosphatemia with iron isomaltoside than have been observed in similarly designed trials of ferric carboxymaltose.

Phosphate is essential in human physiology. An individual with a low serum phosphate level (<0.65 mmol/L) is considered to be at risk of experiencing clinical symptoms including fatigue, proximal muscle weakness, and bone pain. However, only a few case reports have documented specific acute clinical symptoms associated with hypophosphatemia. Furthermore, these symptoms are difficult to distinguish from the clinical manifestations of IBD and iron deficiency/iron deficiency anaemia. If hypophosphatemia is severe, potential complications include respiratory failure, rhabdomyolysis, haemolysis and left ventricular dysfunction. Additionally, an increasing number of published case reports have shown that prolonged hypophosphatemia can result in osteomalacia.

The aim of this study was to investigate the rate of hypophosphatemia after infusion of a single dose of intravenous iron (1000 mg) in adults with IBD treated with either ferric carboxymaltose or iron isomaltoside.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

This prospective observational study was conducted between 1 February 2017 and 1 July 2018. Adult IBD patients (>18 years), including both Crohn’s disease and ulcerative colitis, with iron deficiency were recruited at two separate study sites in the southeast region of Norway. These two study sites use different intravenous iron preparations to treat iron deficiency—ferric carboxymaltose is used at Oslo University Hospital Ullevål and iron isomaltoside is used at Akershus University Hospital. All patients provided written informed consent after receiving oral and written information about the study. The consent was necessary due to Norwegian law, the planned extra study visits and collected study samples; and the registration of data.

Both hospitals have a well-defined catchment area and the two centres do not differ in regard to patient demographics, or diagnostic, treatment and follow-up protocols except in the choice of high-dose intravenous iron treatment. In Norway, all IBD patients are primarily treated in outpatient clinics.

Patients diagnosed with iron deficiency/iron deficiency anaemia (according to the ECCO guidelines), as a consequence of IBD, were eligible for inclusion into the study. The decision to treat with high-dose intravenous iron was made independently of the study. Eligible patients were prescribed 1000 mg of high-dose intravenous iron, ferric carboxymaltose (50 mg/mL) or iron isomaltoside (100 mg/mL), administered as a single dose. Patients who had received high-dose intravenous iron treatment or a packed red blood cell transfusion within 3 months of study entry, or for whom high-dose intravenous iron treatment was contraindicated, were excluded from the study. Patients prescribed ferric carboxymaltose or iron isomaltoside at a dose other than 1000 mg were excluded (to ensure comparable dosing between the two intravenous iron treatment groups). Pregnant or breastfeeding women were also excluded.

Enrolment continued until at least 50 consecutive patients with complete adherence to the study protocol were recruited at each site (a total of more than 100 patients). The enrolment period was followed by a prospective observation period, which lasted ≤7 weeks for each patient and included three study visits.

Study inclusion was performed at baseline, at which time intravenous iron treatment was administered. Patients attended the clinic at week 2 (10-15 days) and at week 6 (5-7 weeks) following intravenous iron treatment. Each patient could receive only one infusion within an approximate 2-month period after consenting to study participation.

2.2 | Study assessments and data collection

Blood analysis at every visit included haemoglobin (Hb), mean corpuscular volume, mean corpuscular Hb, thrombocytes, reticulocytes, reticulocyte Hb content, iron, ferritin, transferrin saturation, transferrin receptor, C-reactive protein (CRP), magnesium, calcium, ionised calcium, creatinine, alkaline phosphatase, albumin, phosphate and vitamin D (25-hydroxyvitamin D).

Faecal calprotectin was measured in stool samples taken within 4 weeks before treatment administration and again in the timeframe of 2 weeks before or 4 weeks after the final visit (Calprotectin ELISA; Buhlmann Laboratories AG, Basel, Switzerland).

Disease activity was assessed at each study visit using the Harvey Bradshaw Index for Crohn’s disease, or the partial Mayo Score for ulcerative colitis.
Information regarding demographic data, such as age, sex, body weight, IBD phenotype and subphenotype, disease history and activity, and previous intravenous iron treatments were collected.

All demographic information was collected from the patient medical records and was systematically entered into an electronic case report form.

Safety was evaluated by recording the number and severity of adverse drug reactions (ADRs). ADRs and pregnancies were registered and reported to the relevant authorities by the investigator, in accordance with the national reporting systems. All events were documented in the patients’ medical notes and in the study records.

The study was completed when all enrolled patients had received intravenous iron administration, had attended all three study visits, and had fulfilled the requirements of the study protocol.

2.3 Study outcomes

The primary endpoint was the proportion of patients with moderate to severe hypophosphatemia, defined as a phosphate level <0.65 mmol/L (or <2.0 mg/dL), following a single 1000 mg intravenous dose of ferric carboxymaltose or iron isomaltoside.

The criteria for hypophosphatemia followed the UK National Health Service (NHS) Guideline for the Treatment of Hypophosphatemia in Adults, published in March 2016. The NHS guidelines categorise hypophosphatemia as mild (serum phosphate level: 0.65-0.79 mmol/L), moderate (0.32-0.64 mmol/L), and severe (<0.32 mmol/L) (normal range: 0.8-1.45 mmol/L).

The key secondary endpoints were to determine the proportion of patients with any hypophosphatemia, to identify possible serologically or clinically related risk factors for the development of hypophosphatemia, and to evaluate response to high-dose (1000 mg) intravenous iron administered in a single dose in regard to iron deficiency/iron deficiency anaemia correction.

2.4 Data analysis

Assuming incidences of hypophosphatemia of 49% with ferric carboxymaltose and 15% with iron isomaltoside (based on data from previous clinical studies) and using a power of 80%, 49 patients per study site were required to detect a difference between ferric carboxymaltose and iron isomaltoside at a significance level of 5%.

Data are presented descriptively for continuous variables, as mean (SD) and median (SD), and as the number of exposed patients (with percentages) for categorical variables.

Differences in proportions were analysed using the Newcomb’s test, and differences in continuous variables were tested using t-tests. The statistical analyses were performed in R.

2.5 Ethical considerations

The study protocol was approved by the relevant local regulatory and ethics committees, and adhered to the applicable laws on data protection. An application was sent to the EudraCT system with the application no. 2016-003476-41 for registration, but the application was deemed to be unnecessary since there were no indications of a medical intervention study.

Study nurses, who interacted with the patients at each study visit, were blinded to the results of laboratory analyses. The primary investigator at each study centre was not blinded for safety reasons, as they did not interact with the patients.

3 RESULTS

The total number of patients recruited and the total number of patients adherent to the study protocol are shown in Figure 1. The demographics of the 52 patients at Oslo University Hospital Ullevål and 54 patients at Akershus University Hospital are shown.

FIGURE 1 Patient flow
in Table 1. There were no significant differences between the two treatment cohorts in terms of demographics, except that there were significantly fewer patients with ulcerative proctitis in the iron isomaltoside treatment group.

Haemoglobin and serum iron parameters at baseline indicate less severe iron deficiency anaemia in the ferric carboxymaltose treatment group compared with the iron isomaltoside treatment group (Table 2). Baseline phosphate levels were lower in the ferric carboxymaltose treatment group, but all within normal range. CRP and faecal calprotectin levels were slightly more elevated in the iron isomaltoside treatment group. Otherwise, the baseline serological data were similar between the treatment groups (Table 2).

With respect to the primary endpoint, at week 2, 56.9% of patients treated with ferric carboxymaltose experienced moderate to severe hypophosphatemia after a single 1000 mg dose compared with 5.7% of the patients treated with iron isomaltoside (P < 0.001). At week 6, 13.7% of patients in the ferric carboxymaltose treatment group continued to demonstrate moderate to severe hypophosphatemia compared with 1.9% in the iron isomaltoside treatment group (P = 0.054; Figure 2 and Table 3). The total incidence of hypophosphatemia (<0.8 mmol/L) was significantly more common with ferric carboxymaltose treatment at weeks 2 and 6 (72.5% and 21.6%, respectively) compared with iron isomaltoside treatment (11.3% and 3.7%, respectively; week 2: P < 0.001, week 6: P = 0.013; Figure 2 and Table 3).

After the end of the predefined observation period, 50% of the patients in the ferric carboxymaltose treatment group were available for subsequent assessment of phosphate levels until normalisation. In this subset of patients, the time to spontaneous normalisation ranged from additionally 1-6 months.

Binary logistic regression analysis did not reveal an association in relation to risk of developing hypophosphatemia, with sex, age, diagnosis, disease phenotype, disease activity, or grade of inflammation, in either the ferric carboxymaltose or the iron isomaltoside treatment groups.

Haemoglobin and serum iron parameters for individual patients in the ferric carboxymaltose and iron isomaltoside treatment groups at baseline and at the follow-up visits are shown in Figure 3A–E. The mean changes from baseline in Hb and serum iron parameters over time after administration of a single 1000 mg dose of ferric carboxymaltose or iron isomaltoside are shown in Figure S1A–E. There was a nonsignificant trend for a greater response to iron isomaltoside treatment compared with ferric carboxymaltose treatment. However, at the end of the study period, <50% of patients in both of the treatment groups met the therapeutic goal of normalised Hb and iron stores.

There were no ADRs registered in this study, except for the development of hypophosphatemia as reported.

### TABLE 1 Patient demographics at baseline

|                | Ferric carboxymaltose (n = 52) | Iron isomaltoside (n = 54) |
|----------------|--------------------------------|-----------------------------|
| Sex, female, n (%) | 29 (55.8)                    | 25 (46.3)                   |
| Age (y), mean (SD) | 40.6 (14.1)                  | 39.5 (13.5)                 |
| IBD phenotype, n (%) |                             |                             |
| Crohn’s disease | 19 (36.5)                     | 28 (51.9)                   |
| Ulcerative colitis | 33 (63.5)                    | 26 (48.1)                   |
| Crohn’s disease subphenotype, n (%)<sup>a</sup> |                             |                             |
| Ileal           | 7 (36.8)                      | 6 (21.4)                    |
| Colonic         | 2 (10.5)                      | 7 (25.0)                    |
| Ileocolonic     | 10 (52.6)                     | 15 (53.6)                   |
| Ulcerative colitis subphenotype, n (%)<sup>b</sup> |                             |                             |
| Ulcerative proctitis | 9 (27.3)                     | 1 (3.8)<sup>c</sup>         |
| Left sided      | 11 (33.3)                     | 5 (19.2)                    |
| Extensive       | 13 (39.4)                     | 20 (76.9)                   |
| Disease duration (y), mean (SD) | 10.6 (9.8) | 11.4 (10.6) |
| Prior surgery, n (%) |                             |                             |
| Yes            | 14 (26.9)                     | 14 (25.9)                   |
| No             | 38 (73.1)                     | 40 (74.1)                   |
| Harvey Bradshaw Index |                   |                             |
| Mean (SD)      | 4.11 (4.7)                    | 5.71 (5.2)                  |
| Median         | 2.0                           | 4.0                         |
| Partial Mayo Score |                           |                             |
| Mean (SD)      | 2.09 (2.3)                    | 2.50 (2.4)                  |
| Median         | 1.0                           | 1.0                         |

<sup>a</sup>Ferric carboxymaltose, n = 19; iron isomaltoside, n = 28; total, n = 47.<br><sup>b</sup>Ferric carboxymaltose, n = 33; iron isomaltoside, n = 26; total, n = 59.<br><sup>c</sup>P < 0.01 vs Ferric carboxymaltose treatment group.

4 | DISCUSSION

The results of this real-world study show a high incidence and persistence of hypophosphatemia in a cohort of IBD patients after administration of a single 1000 mg intravenous dose of ferric carboxymaltose. Hypophosphatemia was observed significantly more frequently in patients receiving ferric carboxymaltose than in those receiving iron isomaltoside, at weeks 2 and 6 after treatment. After 6 weeks, only two patients treated with iron isomaltoside presented with hypophosphatemia; both cases were of mild to moderate severity.

Binary regression analysis did not demonstrate any correlation between hypophosphatemia and grade of inflammation, phenotype and subphenotype of disease, or concomitant medication. Additionally, there was no correlation to baseline phosphate levels and the drop of value or the severity of hypophosphatemia at weeks 2 and 6. The difference in baseline phosphate levels in the two treatment groups seems therefore to have no clinical relevance. The occurrence of hypophosphatemia does not appear to be a side effect of intravenous iron that is unique to patients with IBD.<sup>21</sup> Individuals with iron deficiency anaemia caused by chronic kidney disease appear to be at a lower risk of developing hypophosphatemia after ferric carboxymaltose treatment compared with other aetiologies.<sup>21</sup>
**TABLE 2** Serological and faecal parameters at baseline, and at weeks 2 and 6 after a single 1000 mg intravenous dose of ferric carboxymaltose or iron isomaltoside

|                          | Baseline                                      | Week 2                        | Week 6                        |
|--------------------------|-----------------------------------------------|-------------------------------|-------------------------------|
|                          | Ferric carboxymaltose | Iron isomaltoside | Ferric carboxymaltose | Iron isomaltoside | Ferric carboxymaltose | Iron isomaltoside |
| Hb (g/dL)                | 12.4 (1.6)                                    | 11.6 (1.8)                    | 12.8 (1.4)                    | 12.7 (1.5)                    | 13.3 (1.4)                                    | 13.4 (1.5)                    |
| MCV (fl)                 | 86.5 (6.8)                                    | 81.4 (7.1)                    | 87.9 (6.1)                    | 83.9 (6.4)                    | 89.1 (6.4)                                    | 84.6 (6.3)                    |
| MCH (pg)                 | 28.1 (3.0)                                    | 26.0 (2.9)                    | 28.5 (2.9)                    | 27.0 (2.6)                    | 29.2 (2.7)                                    | 27.7 (2.5)                    |
| Thrombocytes (10^9/L)    | 330.4 (113.1)                                 | 334.0 (108.6)                 | 316.8 (106.4)                 | 299.5 (76.0)                  | 302.2 (106.6)                                 | 281.4 (87.2)                  |
| Reticulocytes (10^9/L)   | 57.8 (19.9)                                   | 45.9 (15.9)                   | 91.3 (31.0)                   | 71.9 (25.0)                   | 63.3 (25.0)                                   | 43.4 (17.5)                   |
| Reticulocyte Hb content (pg) | 29.9 (4.1)                                | 25.6 (5.6)                    | 32.7 (3.4)                    | 32.0 (3.9)                    | 32.4 (4.0)                                    | 31.2 (3.7)                    |
| Iron (μmol/L)            | 11.2 (6.1)                                    | 8.3 (5.8)                     | 16.2 (6.7)                    | 15.3 (6.7)                    | 16.3 (6.5)                                    | 13.4 (6.6)                    |
| Transferrin saturation (%) | 15.4 (7.9)                                 | 10.8 (7.4)                    | 27.0 (10.6)                   | 24.2 (10.4)                   | 28.5 (11.5)                                   | 22.3 (11.8)                   |
| Transferrin receptor (mg/L) | 4.0 (2.3)                                  | 6.5 (4.6)                     | 3.2 (2.4)                     | 4.8 (3.4)                     | 3.2 (2.3)                                     | 3.7 (3.0)                     |
| Ferritin (μg/L)          | 24.3 (21.9)                                   | 19.6 (28.0)                   | 494.2 (204.9)                 | 316.1 (139.7)                 | 192.8 (107.1)                                 | 126.6 (90.7)                  |
| CRP (mg/L)               | 3.4 (4.1)                                     | 7.3 (12.4)                    | 3.3 (4.9)                     | 4.9 (7.6)                     | 3.2 (4.8)                                     | 4.8 (6.2)                     |
| CRP (mg/L), median (SD)  | 1.8 (4.1)                                     | 2.0 (12.4)                    | 1.2 (1.9)                     | 1.0 (7.6)                     | 1.4 (1.8)                                     | 2.0 (6.2)                     |
| Creatinine (μmol/L)      | 70.7 (13.2)                                   | 73.2 (14.4)                   | 65.3 (12.3)                   | 74.7 (14.6)                   | 69.9 (13.7)                                   | 75.5 (14.4)                   |
| ALP (U/L)                | 78.2 (39.9)                                   | 76.3 (32.2)                   | 78.2 (34.4)                   | 78.5 (36.9)                   | 76.4 (33.2)                                   | 77.4 (37.5)                   |
| Calcium (mmol/L)         | 2.31 (0.11)                                   | 2.33 (0.12)                   | 2.24 (0.08)                   | 2.35 (0.12)                   | 2.33 (0.11)                                   | 2.36 (0.19)                   |
| Ionised calcium (mmol/L) | 1.21 (0.05)                                   | 1.23 (0.04)                   | 1.20 (0.04)                   | 1.23 (0.05)                   | 1.21 (0.05)                                   | 1.25 (0.05)                   |
| Magnesium (mmol/L)       | 0.84 (0.07)                                   | 0.82 (0.08)                   | 0.83 (0.06)                   | 0.84 (0.08)                   | 0.84 (0.07)                                   | 0.83 (0.08)                   |
| Phosphate (mmol/L)       | 1.07 (0.17)                                   | 1.15 (0.17)                   | 0.65 (0.25)                   | 1.07 (0.24)                   | 1.00 (0.29)                                   | 1.14 (0.20)                   |
| Albumin (g/L)            | 42.7 (4.4)                                    | 41.7 (4.0)                    | 43.3 (3.8)                    | 42.5 (4.0)                    | 44.2 (4.2)                                     | 42.8 (4.5)                    |
| 25-hydroxyvitamin D (nmol/L) | 58.3 (24.4)                             | 63.5 (21.9)                   | 57.1 (23.1)                   | 64.6 (20.0)                   | 57.5 (20.8)                                   | 62.8 (21.1)                   |
| Faecal calprotectin (mg/kg) | 851 (1100)                                 | 1040 (1365)                   | NA                           | NA                           | 726 (1205)                                   | 707 (956)                     |
| Faecal calprotectin (mg/kg), median (SD) | 298 (1100)                               | 562 (1365)                    | NA                           | NA                           | 364 (1205)                                   | 318 (956)                     |

Values are mean (SD) unless otherwise stated.
Abbreviations: ALP, alkaline phosphatase; CRP, C-reactive protein; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; NA, not applicable; SD, standard deviation.

**FIGURE 2** Phosphate levels in IBD patients with iron deficiency/iron deficiency anaemia at baseline and at weeks 2 and 6 after a single 1000 mg intravenous dose of ferric carboxymaltose or iron isomaltoside. Horizontal bars represent group medians.
FIGURE 3 A-E. Haemoglobin and serum iron parameters in IBD patients with iron deficiency/iron deficiency anaemia at baseline and at weeks 2 and 6 after a single 1000 mg intravenous dose of ferric carboxymaltose or iron isomaltoside. Horizontal bars represent group medians.
However, in this study, all patients had creatinine values within the normal range.

This study demonstrates that ferric carboxymaltose and iron isomaltoside are both effective in the correction of iron deficiency and iron deficiency anaemia. The nonsignificant trend for greater effectiveness observed with iron isomaltoside treatment may be due to lower mean Hb levels and more severe iron deficiency at baseline in the iron isomaltoside treatment group compared with the ferric carboxymaltose treatment group. However, at the end of the study period, <50% of patients in both of the treatment groups met the therapeutic goal of normalised Hb and iron stores. When the simplified dosing method is used to calculate the iron need (see the ECCO guidelines), patients with iron deficiency/iron deficiency anaemia can be assigned to one of four dosing groups (see Table 4). In this study, the majority of patients had an iron need >1000 mg before treatment (Table 4). Compared with the ferric carboxymaltose treatment group, a greater proportion of the patients in the iron isomaltoside treatment group had an iron need >1000 mg (Table 4). At 6 weeks following administration of 1000 mg intravenous iron, 58% of patients needed additional iron supplementation (Table 4). These findings are in accordance with the results of the NiMo study that showed a trend towards underdosing of iron at a dose of 1000 mg.35

Anaemia is one of the most common extra-intestinal manifestations in IBD,1 and one of the most common health-related problems worldwide.36 Awareness of the benefits of treating iron deficiency and iron deficiency anaemia with high-dose intravenous iron across various medical and surgical conditions is steadily increasing, with improvements reported in patient quality of life and disease outcomes, and reductions in morbidity.37-39 However, the finding in this study of persistent moderate to severe hypophosphatemia beyond 6 weeks after intravenous iron treatment with ferric carboxymaltose is a clinical concern that requires further investigation.
If ferric carboxymaltose is considered for use to correct iron deficiency or iron deficiency anaemia in a clinical setting, it is important to measure serum phosphate concentrations before treatment. If the patient has pre-existing hypophosphatemia, ferric carboxymaltose should be avoided. Monitoring serum phosphate concentrations at 2 and 6 weeks after treatment with intravenous iron is reasonable, in order to identify patients that need close follow-up or phosphate supplementation until normalisation of phosphate levels. However, the mechanism associated with the development of hypophosphatemia after ferric carboxymaltose treatment involves increased urinary phosphate excretion resulting from increased circulating concentrations of fibroblast growth factor 23 (FGF23), rendering sustainable correction of hypophosphatemia by oral or intravenous phosphate administration very difficult.

Repeated infusions with ferric carboxymaltose probably increase the risk of developing severe symptoms of hypophosphatemia, such as osteomalacia. Therefore, it is important to investigate bone and muscle pain reported by patients with chronic conditions, such as IBD, who may be receiving repeated infusions of high-dose intravenous iron. In this study, there were no reports of specific symptoms related to hypophosphatemia during the observation period.

In general, monitoring phosphate levels for longer than 6 weeks after administration of intravenous iron may be unnecessary. However, it is important to consider longer term monitoring of phosphate levels in certain at-risk patient populations. This may be particularly valuable in patients who receive repeated infusions and in circumstances where hypophosphatemia is relevant in the short term, for example, pre-operative optimisation.

Potential limitations of this study include the lack of specific questionnaires for hypophosphatemia-related symptoms or physical tests for hypophosphatemia. Therefore, methods of detecting the condition are limited to blood sampling and urine testing. Although, since only the results of the laboratory tests were analysed, this could be considered a strength as this potentially reduces subjective bias. However, not all study personnel were blinded to the results of the biochemical analysis. Another potential limitation of the study is that only one of the intravenous iron manufacturers invited to support this study agreed to be involved.

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Author contributions: Trond Espen Detlie: planned, designed and conducted the study, interpreted the data, drafted and critically revised the manuscript. Jonas Christoffer Lindström: performed the statistical analysis and critically revised the manuscript. Marte Eide Jahnsen: conducted the study and critically revised the manuscript. Elisabeth Finnes: conducted the study and critically revised the manuscript. Heinz Zoller: interpreted the data, helped to draft and critically revised the manuscript. Bjørn Moum: contributed to the design and conducted the study, interpreted the data, helped to draft and critically revised the manuscript. Jørgen Jahnsen: planned, designed and conducted the study, interpreted the data, helped to draft and critically revised the manuscript. All authors approved the final version of this article, including the authorship list.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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