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Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with iron isomaltoside or ferric carboxymaltose: results of a prospective cluster randomised cohort study

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Background

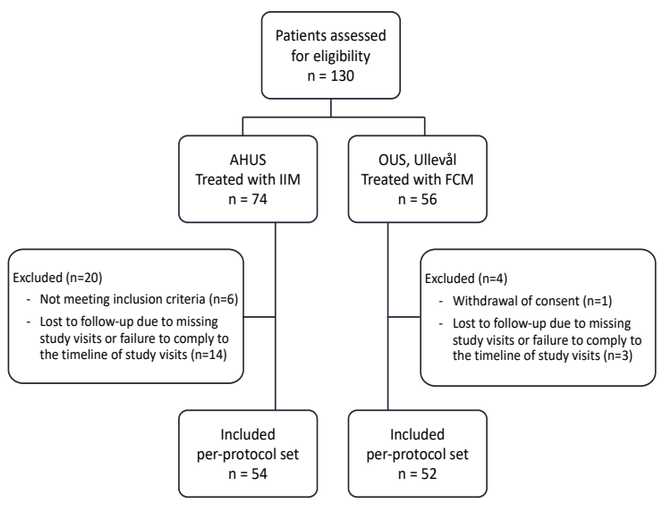
Iron deficiency (ID) and iron deficiency anemia (IDA) are common complications in inflammatory bowel disease (IBD). ECCO guideline states that high dose IV iron is the treatment of choice. Ferric carboxymaltose (FCM; Ferinject®) and iron isomaltoside (IIM; Monofer®) are the high-dose iron preparations used in Europe. Hypophosphatemia is a reported side effect of both preparations and may give symptoms similar to clinical manifestations of IBD and ID/IDA. Previous publications suggest a higher risk of hypophosphatemia after FCM than IIM, but this has not yet been explored in prospective head-to-head studies.

In this trial we investigate the occurrence of hypophosphatemia in an adult IBD population treated with either FCM or IIM.

Methods

A prospective cluster-randomized comparative two-center study was conducted at Akershus University Hospital (AHUS) and Oslo University Hospital Ullevål (OUS Ullevål) over 1.5-years involving adult IBD patients with ID or IDA. Patients presenting at AHUS were treated with 1000 mg IIM and at OUS Ullevål they received 1000 mg FCM. At baseline, after 2- and 6-weeks clinical assessment of muscle function, quality of life, faecal-, blood- and urine- tests were collected.

Results



Results of the serological- and faecal samples taken at inclusion, visit after 14 days and 5-7 weeks

Test	Inclusion			Follow-up 2 weeks		Follow-up 5-7 weeks	
	Ferinject	Monofer	p-value	Ferinject	Monofer	Ferinject	Monofer
Hemoglobin (Hb) g/dL, Mean (SD)	12.4 (1.6)	11.6 (1.8)	0.019	12.8 (1.4)	12.7 (1.5)	13.3 (1.4)	13.4 (1.5)
MCV fL, Mean (SD)	86.5 (6.8)	81.4 (7.1)	0.000	87.9 (6.1)	83.9 (6.4)	89.1 (6.4)	84.6 (6.3)
MCH pg, Mean (SD)	28.1 (3.0)	26.0 (2.9)	0.000	28.5 (2.9)	27.0 (2.6)	29.2 (2.7)	27.7 (2.5)
Thrombocytes x10^9/L, Mean (SD)	330.4 (113.1)	334.0 (108.6)	0.867	316.8 (106.4)	299.5 (76.0)	302.2 (106.6)	281.4 (87.2)
Reticulocytes x10^9/L, Mean (SD)	57.8 (19.9)	45.9 (15.9)	0.001	91.3 (31.0)	71.9 (25.0)	63.3 (25.0)	43.4 (17.5)
Reticulocyte Hb Content/CHr pg, Mean (SD)	29.9 (4.1)	25.6 (5.6)	0.000	32.7 (3.4)	32.0 (3.9)	32.4 (4.0)	31.2 (3.7)
Iron µmol/L, Mean (SD)	11.2 (6.1)	8.3 (5.8)	0.015	16.2 (6.7)	15.3 (6.7)	16.3 (6.5)	13.4 (6.6)
Transferrin saturation %, Mean (SD)	15.4 (7.9)	10.8 (7.4)	0.003	27.0 (10.6)	24.2 (10.4)	28.5 (11.5)	22.3 (11.8)
Transferrin receptor mg/L, Mean (SD)	4.0 (2.3)	6.5 (4.6)	0.001	3.2 (2.4)	4.8 (3.4)	3.2 (2.3)	3.7 (3.0)
Ferritin µg/L, Mean (SD)	24.3 (21.9)	19.6 (28.0)	0.335	494.2 (204.9)	316.1 (139.7)	192.8 (107.1)	126.6 (90.7)
CRP mg/L, Mean (SD)	3.4 (4.1)	7.3 (12.4)	0.033	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, Mean (SD)	70.7 (13.2)	73.2 (14.4)	0.358	65.3 (12.3)	74.7 (14.6)	69.9 (13.7)	75.5 (14.4)
ALP U/L, Mean (SD)	78.2 (39.9)	76.3 (32.2)	0.778	78.2 (34.4)	78.5 (36.9)	76.4 (33.2)	77.4 (37.5)
Calcium mmol/L, Mean (SD)	2.31 (0.11)	2.33 (0.12)	0.447	2.24 (0.08)	2.35 (0.12)	2.33 (0.11)	2.36 (0.19)
Ionized Calcium mmol/L, Mean (SD)	1.21 (0.05)	1.23 (0.04)	0.011	1.20 (0.04)	1.23 (0.05)	1.21 (0.05)	1.25 (0.05)
Magnesium mmol/L, Mean (SD)	0.84 (0.07)	0.82 (0.08)	0.287	0.83 (0.06)	0.84 (0.08)	0.84 (0.07)	0.83 (0.08)
Phosphate mmol/L, Mean (SD)	1.07 (0.17)	1.15 (0.17)	0.030	0.65 (0.25)	1.07 (0.24)	1.00 (0.29)	1.14 (0.20)
Albumin g/L, Mean (SD)	42.7 (4.4)	41.7 (4.0)	0.195	43.3 (3.8)	42.5 (4.0)	44.2 (4.2)	42.8 (4.5)
Vitamin 25(OH)D nmol/L, Mean (SD)	58.3 (24.4)	63.5 (21.9)	0.257	57.1 (23.1)	64.6 (20.0)	57.5 (20.8)	62.8 (21.1)
Fecal calprotectin mg/kg, Mean (SD)	851 (1100)	1040 (1365)	0.478	NA	NA	726 (1205)	707 (956)
Fecal calprotectin mg/kg, Median	298 (1100)	562 (1365)	-	NA	NA	364 (1205)	318 (956)

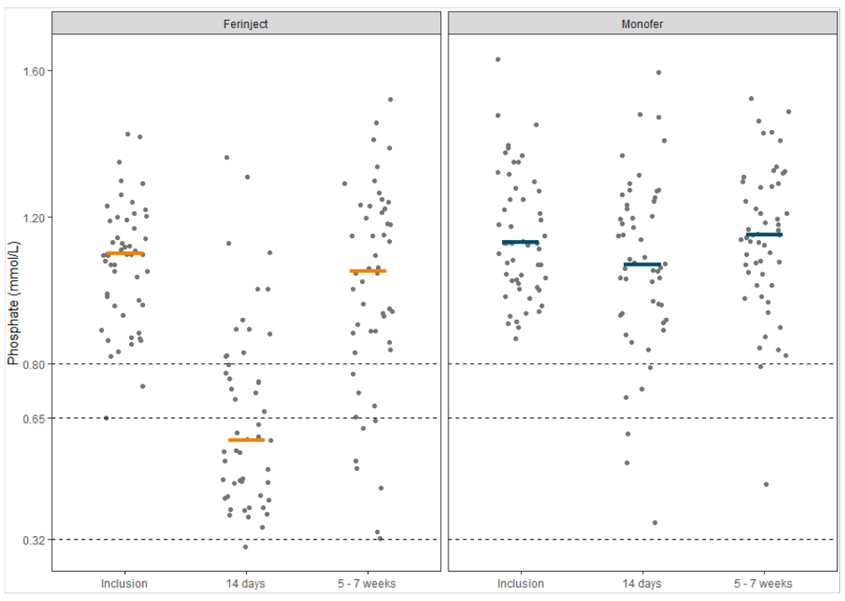
Patient demographics

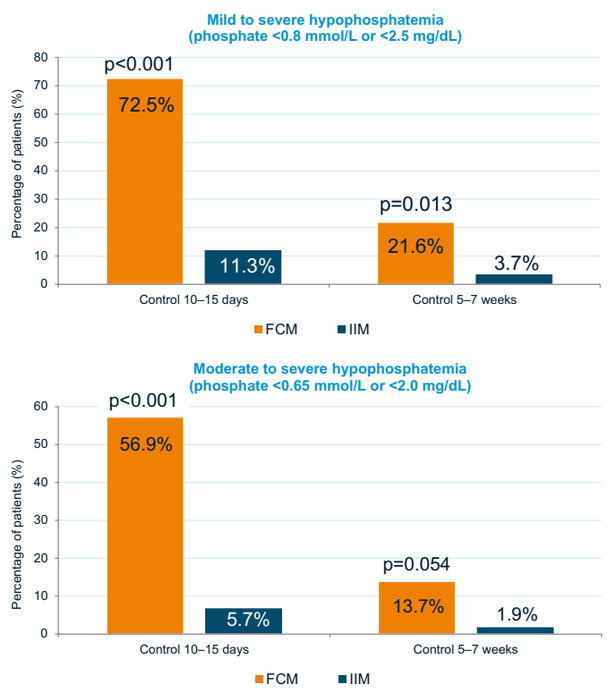
		Ferinject	Monofer	Total
N		52	54	106
Sex	Women (%)	29 (56%)	25 (46%)	54 (51%)
	Men (%)	23 (44%)	29 (54%)	52 (49%)
Age	Mean (SD)	40.6 (14.1)	39.5 (13.5)	40.1 (13.7)
IBD	CD (%)	19 (37%)	28 (52%)	47 (44%)
	UC (%)	33 (63%)	26 (48%)	59 (56%)
CD extension	Ileal (%)	7 (37%)	6 (21%)	13 (28%)
	Colonic (%)	2(11%)	7 (25%)	9 (19%)
	Ileocolonic (%)	10 (53%)	15 (54%)	25 (53%)
UC extension*	Ulcerative proctitis (%)	9 (27%)	1 (4%)	10 (17%)
	Left sided UC (%)	11 (33%)	5 (19%)	16 (27%)
	Extensive UC (%)	13 (39%)	20 (77%)	33 (56%)
Disease duration	Years, Mean (SD)	10.6 (9.8)	11.4 (10.6)	11.0 (10.2)
Prior surgery	Yes (%)	14 (27%)	14 (26%)	28 (26%)
	No (%)	38 (73%)	40 (74%)	78 (74%)
HBI	Mean (SD)	4.11 (4.7)	5.71 (5.2)	5.09 (5.02)
	Median	2.0	4.0	
PMS	Mean (SD)	2.09 (2.3)	2.50 (2.4)	2.28 (2.28)
	Median	1.0	1.0	

*There was a significant difference in UC extension between the two treatment groups (p< 0.01)
N= Number of patients, IBD= Inflammatory bowel disease, CD= Crohn`s disease, UC= Ulcerative colitis, HBI= Harvey Bradshaw Index, PMS= Partial Mayo Score, SD= Standard deviation

Comparison of the phosphate results in the two different high dose i.v. iron treatment arms after 14 days and 5-7 weeks

Time	Phosphate level	Ferric carboxymaltose (FCM; Ferinject®) No. of patients	Iron isomaltoside (IIM; Monofer®) No. of patients
Visit 2 (14 days)	Normal (≥ 0.8 mmol/L)	13 (25%)	47 (89%)
	Mild (0.65 - <0.8 mmol/L)	9 (18%)	3 (6%)
	Moderate (0.32 - <0.65 mmol/L)	28 (55%)	3 (6%)
	Severe (<0.32 mmol/L)	1 (2%)	0 (0%)
	Missing	1	1
Visit 3 (5-7 weeks)	Normal (≥ 0.8 mmol/L)	40 (78%)	52 (96%)
	Mild (0.65 - <0.8 mmol/L)	3 (6%)	1 (2%)
	Moderate (0.32 - <0.65 mmol/L)	7 (14%)	1 (2%)
	Severe (<0.32 mmol/L)	1 (2%)	0 (0%)
	Missing	1	0





Conclusion

In a real life IBD patient cohort we found a high incidence, severity and duration of hypophosphatemia after administration of a single IV dose of 1000 mg FCM but not after 1000 mg IIM. The presence of moderate to severe hypophosphatemia beyond 6 weeks is a clinical concern that needs further investigation. After the end of the predefined observation period 50% of the patients in the FCM treatment arm were available for subsequent assessment with phosphate levels until normalization. In this group, time of spontaneous normalization ranged from 1 to 6 months.