Rev Nefrol Dial Traspl. 2026;46(3):140-150

The effect of Ferric Carboxymaltose on Inflammation: Comparison of Different Glomerular Filtratıon Rate and Dose Groups

El Efecto del Carboximaltosa Férrica sobre la Inflamación: Comparación de Diferentes Grupos de Tasa de Filtración Glomerular y Dosis

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is frequently complicated by iron deficiency anemia, which adversely affects prognosis. Ferric carboxymaltose (FCM) is an effective intravenous iron therapy; however, concerns exist regarding its effects on inflammation. Composite indices such as the systemic immune-inflammation index (SII), pan-immune-inflammation value (PIV), and hemoglobin-albumin-lymphocyte-platelet (HALP) score provide broader insights into immunonutritional status and systemic inflammation. **Objectives**: To evaluate the effects of intravenous FCM therapy on biochemical parameters and novel inflammatory indices (SII, PIV, HALP), and to investigate whether these effects differ according to glomerular filtration rate (GFR) and dose groups**. Materials and Methods**: This retrospective, single-center study included 204 patients with iron-deficiency anemia who received FCM at 500 mg or 1000 mg. Laboratory values were assessed before and two weeks after treatment. Patients were stratified by GFR (<60 vs. ≥60 ml/min/1.73 m²). Changes in hematological, biochemical, and inflammatory indices were analyzed using appropriate statistical tests, including multiple-comparisons corrections. **Results:** FCM significantly improved hemoglobin, hematocrit, ferritin, serum iron, and transferrin saturation (all $p<0.001$). HALP increased (0.20→0.29; $p<0.001$), while PIV decreased (384→325; $p<0.001$) and SII showed a modest reduction (731→615; $p=0.040$). GFR ≥60 patients exhibited greater improvements in hematological parameters. No independent association was observed between GFR and inflammatory indices. Dose groups (500 vs. 1000 mg) showed comparable effects. **Conclusions**: IV FCM therapy improved anemia-related parameters and favorably modulated inflammatory indices, suggesting potential benefits beyond iron replacement. The absence of dose-dependent differences indicates that lower doses may be sufficient. Prospective studies with longer follow-up are warranted.

Keywords: Ferric carboxymaltose; Systemic immune-inflammation index; Pan-immune-inflammation value; Hemoglobin-Albumin-

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Financiamiento:
Ninguno.

Conflicto de intereses:
Ninguno que declarar.

Recibido: 26-09-2025
Corregido: 20-06-2026
Aceptado: 15 -07-2026

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ISSN 0326-3428

Lymphocyte-Platelet score; Chronic kidney disease; Inflammation; Biomarkers.

RESUMEN

Introducción: La enfermedad renal crónica (ERC) se asocia con frecuencia a anemia por deficiencia de hierro, lo que empeora el pronóstico. La carboximaltosa férrica (FCM) es un tratamiento intravenoso eficaz; sin embargo, existen dudas sobre sus efectos inflamatorios. Índices compuestos como el índice sistémico de inflamación-inmunidad (SII), el valor pan-inmune-inflamatorio (PIV) y la puntuación hemoglobina-albúmina-linfocito-plaqueta (HALP) ofrecen una visión integral del estado inmunonutricional y de la inflamación sistémica. **Objetivos:** Evaluar los efectos de la FCM intravenosa sobre parámetros bioquímicos e índices inflamatorios novedosos (SII, PIV, HALP), y determinar si estos efectos difieren según la tasa de filtración glomerular (TFG) y el grupo de dosis. **Materiales y Métodos:** Estudio retrospectivo unicéntrico con 204 pacientes con anemia ferropénica tratados con FCM (500 o 1000 mg). Se evaluaron valores de laboratorio antes y dos semanas después del tratamiento. Los pacientes se estratificaron por TFG (<60 vs. ≥60 ml/min/1,73 m²). Los cambios en parámetros hematológicos, bioquímicos e índices inflamatorios se analizaron con pruebas estadísticas apropiadas y correcciones por comparaciones múltiples. **Resultados:** La FCM mejoró significativamente la hemoglobina, hematocrito, ferritina, hierro sérico y saturación de transferrina (todos p<0,001). El HALP aumentó (0,20→0,29; p<0,001), mientras que el PIV disminuyó (384→325; p<0,001) y el SII mostró una reducción modesta (731→615; p=0,040). Los pacientes con TFG ≥60 presentaron mayores mejorías hematológicas. No se halló asociación independiente entre TFG e índices inflamatorios. Los grupos de dosis (500 vs. 1000 mg) mostraron efectos comparables. **Conclusiones:** La FCM intravenosa mejoró parámetros relacionados con la anemia y moduló favorablemente los índices inflamatorios, lo que sugiere beneficios más allá de la reposición de hierro. La ausencia de diferencias según la dosis indica que dosis menores podrían ser suficientes. Se requieren estudios prospectivos con seguimiento prolongado.

Palabras clave: Carboximaltosa férrica; índice de inflamación sistémica; Score hemoglobina-albúmina-linfocitos-plaquetas.

INTRODUCTION

Chronic kidney disease (CKD) is a major health problem worldwide, with an increasing prevalence and a high risk of mortality [1]. One of the most common complications of CKD is iron deficiency. Iron deficiency is one of the most important causes of anemia, increasing the risk of cardiovascular events, reducing quality of life, and adversely affecting prognosis [2]. Therefore, the effective and safe treatment of iron deficiency is a key component of CKD management.

Although oral iron preparations are generally the first-line treatment, intravenous (IV) iron therapies are preferred in cases such as gastrointestinal intolerance, malabsorption, or the need for rapid replacement [3]. Ferric carboxymaltose (FCM), owing to its ability to be administered at high doses, long half-life, and good tolerability, stands out as an effective treatment option, particularly in patients with CKD [4,5].

CKD is also a disease accompanied by systemic inflammation. During the inflammatory process, levels of cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6), and TNF-α increase; these markers are closely associated with both disease severity and cardiovascular mortality [6]. In addition, simple indices based on hematological parameters, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), have been proposed as practical biomarkers reflecting inflammation in CKD [7].

In recent years, more comprehensive and integrative indicators have been developed. Composite parameters such as the Systemic Immune-Inflammation Index (SII), the Pan-Immune-Inflammation Value (PIV), and the Hemoglobin-Albumin-Lymphocyte-Platelet (HALP) score reflect not only the inflammatory response but also the hematological and immunonutritional status[8]. These indices have been reported to show strong associations with mortality and morbidity in various malignancies and chronic diseases [8,10].

Although there are concerns that IV iron

therapies may increase inflammation, FCM has been suggested to be safer compared to other iron preparations due to its stable structure and pharmacokinetic properties [11,12]. However, there are limited data in the literature on differences in inflammatory responses by glomerular filtration rate (GFR) and on the effects of different ferric carboxymaltose (FCM) doses on inflammatory parameters.

OBJECTIVES

The aim of this study was to evaluate the effects of IV FCM therapy on biochemical parameters and novel inflammatory indices (SII, PIV, HALP), and to investigate potential differences in these effects between different GFR levels and dosage groups.

MATERIALS AND METHODS

Study Design and Population

This retrospective, single-center observational study included the data of 204 patients who received IV FCM treatment at the Department of Internal Medicine and Nephrology, Harran University Faculty of Medicine, between July 2023 and September 2024. Patients aged ≥18 years with a diagnosis of iron deficiency anemia were included in the study.

Inclusion criteria:

-Diagnosis of iron deficiency anemia,

-Receiving intravenous FCM therapy (500 mg or 1000 mg),

-Availability of laboratory data before and two weeks after treatment.

Exclusion criteria:

-Hematological malignancy

-Acute infection

-Acute kidney injury

-End-stage renal disease requiring dialysis.

Treatment and Dosage

All patients received FCM at a total dose calculated according to their iron deficit. The iron requirement was determined based on body weight and baseline hemoglobin level using the Ganzoni formula [13]:

Iron requirement (m g) = Body weight (k g) × (Target Hb − Actual Hb, g/L) × 0.24 + Iron stores (≈500 mg).

According to the calculated iron deficit, patients received either 500 mg or 1000 mg of FCM. The maximum dose administered in a single session was limited to 1000 mg [13].

Glomerular Filtration Rate Grouping

Patients were stratified into two groups according to GFR: <60 and ≥60 ml/min/1.73 m². GFR was calculated using the CKD-EPI formula [14]. The diagnosis of chronic kidney disease was based on a GFR <60 ml/min/1.73 m² calculated by CKD-EPI and persisting for at least 3 months. The cutoff of GFR <60 ml/min/1.73 m² was chosen to represent moderate-to-advanced kidney dysfunction (G3 or higher) according to KDIGO staging [15].

Data collection

Demographic characteristics (age, sex, comorbidities, medications) and biochemical parameters (urea, creatinine, sodium, potassium, calcium, phosphorus, albumin, CRP, AST, ALT, ALP, GGT, ferritin, transferrin saturation, total iron-binding capacity [TIBC], vitamin B12, folate) were recorded. Hematological parameters (hemoglobin, hematocrit, leukocytes, neutrophils, lymphocytes, platelets) were evaluated. Electrolyte changes were specifically examined for calcium, phosphorus, sodium, and potassium. To assess biochemical differences between GFR and dose groups, the change (Δ = pre-treatment − post-treatment) was calculated for each parameter, and group comparisons were performed using these change values.

Immune-Inflammatory Indices

Three composite inflammatory indices were calculated:

-Systemic Immune-Inflammation Index (SII) = (Neutrophils × Platelets) / Lymphocytes

-Pan-Immune-Inflammation Value (PIV) = (Neutrophils × Monocytes × Platelets) / Lymphocytes

-Hemoglobin-Albumin-Lymphocyte-Platelet (HALP) score = (Hemoglobin × Albumin × Platelets) / Lymphocytes

These indices have been shown in the literature to reflect not only inflammatory responses but also immunonutritional status, and to have prognostic value in various clinical settings [8,10,16]

 ISSN 0326-3428

Follow-up Period

The second week after treatment was chosen as the follow-up point, as this time frame is frequently used in studies showing early increases in hemoglobin following FCM therapy [17]. In addition, systematic observations have demonstrated that IV iron therapy can begin to affect biochemical parameters in the early period (approximately 1–2 weeks) [18].

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For normally distributed paired data, paired t-tests were used, while the Wilcoxon test was applied for non-normally distributed paired data. For independent group comparisons, independent t-tests or Mann–Whitney U tests were used as appropriate. Categorical variables were compared using the chi-square test. Normally distributed continuous variables were presented as mean ± standard deviation, while non-normally distributed variables were expressed as median (minimum–maximum). A p-value <0.05 was considered statistically significant, and all tests were two-tailed.

Because multiple comparisons were made for biochemical and hematological parameters before and after treatment, Bonferroni and Benjamini–Hochberg (FDR) corrections were applied to reduce the risk of type I error. The same approach was used to compare GFR subgroups (<60 and ≥60 ml/min/1.73 m²) and dose groups (500 mg and 1000 mg). Only findings with p <0.001 were considered statistically significant after these corrections.

Additionally, possible associations between GFR (<60 and ≥60 ml/min/1.73 m²) and changes in inflammatory markers (HALP, PIV, SII) were evaluated using linear and logistic regression models. For logistic regression analyses, dependent variables were dichotomized at the median change (increase vs. no increase; decrease vs. no decrease). All tests were performed two-tailed.

ETHICS APPROVAL

Ethics approval was obtained for this study (Decision No: HRÜ/24.20.54).

RESULTS

A total of 204 patients were included in the study, with a median age of 41 years (18–84), and 81.4% were female. Of these, 69.6% (n=142) received 1000 mg of ferric carboxymaltose (FCM) and 30.4% (n=62) received 500 mg. The glomerular filtration rate (GFR) was <60 ml/min/1.73 m² in 18.9% of participants (n=37) and ≥60 ml/min/1.73 m² in 81.1% (n=167).

A comparison of laboratory parameters obtained two weeks after FCM treatment with baseline values demonstrated that hemoglobin increased from 8.8 to 11.1 g/dL, hematocrit from 28.6% to 35.0%, ferritin from 3 to 127 ng/mL, transferrin saturation from 4.1% to 28.4%, and serum iron from 17 to 62 µg/dL, while total iron-binding capacity (TIBC) decreased from 389 to 224 µg/dL, and ALT and GGT levels increased (all p<0.001). Among immunonutritional scores, HALP increased from 0.20 to 0.29 (p<0.001), while PIV decreased from 384 to 325 (p<0.001). All these changes remained statistically significant after Bonferroni correction.

Regarding electrolytes, sodium increased from 138 to 140 mmol/L (p<0.001) and calcium from 8.9 to 9.1 mg/dL (p<0.001), while phosphorus decreased from 3.6 to 3.4 mg/dL (p=0.015). No significant change was observed in potassium (p=0.180). After Bonferroni correction, only the changes in sodium and calcium remained statistically significant.

In nominal analyses, a slight decrease in phosphorus (3.6 to 3.4 mg/dL; p=0.015), a reduction in SII (731 to 615; p=0.040), an increase in albumin (4.0 to 4.2 g/dL; p=0.012), a decrease in folate (8.1 to 7.0 ng/mL; p=0.110), and an increase in vitamin B12 (265 to 305 pg/mL; p=0.026) were observed. However, these differences lost significance after Bonferroni correction, while with Benjamini–Hochberg (FDR) correction, the changes in phosphorus, albumin, B12, and SII remained significant.

When GFR subgroups were compared, after multiple corrections only the changes in hemoglobin, hematocrit, serum iron, and TIBC remained significant between groups (all p<0.001). The increase in serum iron was greater in the higher GFR group (−48.5 vs. −16 µg/dL; p<0.001), and the reduction in TIBC was

also more pronounced in this group (+155.1 vs. +55.3 µg/dL; p<0.001). Although hemoglobin and hematocrit increased significantly in both groups, the increase was more pronounced in patients with GFR ≥60 ml/min/1.73 m² (Hb +2.56 vs. +1.27 g/dL; Hct +6.97 vs. +4.09%; both p<0.001). For other parameters (e.g., AST, folate, PIV), differences were observed at the nominal level, but they were not significant after multiple comparison corrections.

Logistic regression analysis was performed to evaluate the relationship between GFR (<60 and ≥60 ml/min/1.73 m²) and changes in inflammatory markers, and showed that GFR was not independently associated with changes in HALP, SII, or PIV scores (all p>0.05). Thus, GFR was not identified as an independent determinant of post-treatment changes in inflammatory markers.

When dose groups were compared, only TIBC showed a nominally significant difference between patients receiving 500 mg and 1000 mg of FCM (p=0.040); however, this difference lost significance after multiple corrections. The findings are summarized in **Table 1** and **Table 2.**

Table 1. Biochemical Measurements Before and After Ferric Carboxymaltose Therapy

	Öncesi	Sonrası	p
BUN (mg/dL)	27,82 (5- 224,7)	27,82 (5-248,24)	0,562[x]
Creatinine (mg/dL)	0,71 (0,23- 7,74)	0,71 (0,19-10,5)	0,378[x]
GFR (ml/dk/1,73 m^2)	107 (6- 166)	106 (5-171)	0,156[x]
Sodium (mEq/L)	138 (125-146)	140 (124-146)	<0,001[x]
Potasium (mEq/L)	4,4 (2,24-6,54)	4,4 (3,1-6,68)	0,180[x]
Calcium (mg/dL)	8,8 (5,87-11)	9,1 (4,66-11,2)	<0,001[x]
Phosphorus (mg/dL)	3,6 (1,6-8)	3,4 (1,2-8,5)	0,015[x]
Albumin (g/L)	4 (1,9-4,9)	4,1 (1,1-5,2)	0,012[x]
CRP (mg/L)	0,67 (0-25,64)	0,52 (0-27,35)	0,544[x]
AST (u/L)	20 (7-143)	20 (1-155)	0,389[x]
ALT (ıu/L)	15 (6-179)	18 (4-274)	<0,001[x]
ALP (ıu/L)	69 (27-458)	74 (22-287)	0,051[x]
GGT (ıu/L)	14 (1-809)	20 (6-470)	<0,001[x]
Iron (mcg/dL)	17 (2-100)	62,5 (12-221)	<0,001[x]
TIBC (mcg/dL)	389,09 (97,26 - 591,15)	224,24 (58,03 - 431,47)	<0,001[x]
TS (%)	4,1 (0 - 77,63)	28,36 (0 - 209,64)	<0,001[x]
Ferritin (ng/mL)	3 (0,2 - 239,7)	127,1 (1,2 - 988,6)	<0,001[x]
Folate (ng/mL)	8,13 (3,65 - 24)	7,06 (2,48 - 24)	0,110[x]
B12 (pg/mL)	322,5 (110 - 1030)	352 (139 - 1942)	0,026[x]
HGB (g/dL)	8,8 (1,98 - 13,25)	11,06 (5,69 - 15,8)	<0,001[x]
HCT (%)	28,58 ± 4,64	35,01 ± 5,36	<0,001[y]
SII	731,16 (55,4 - 6507,89)	614,92 (75,81 - 11289,59)	0,040[x]
PIV	384,08 (32,22 - 4878,72)	324,6 (24,36 - 8701,14)	<0,001[x]
HALP	0,2 (0,03 - 1,94)	0,29 (0,03 - 1)	<0,001[x]

x: Wilcoxon test; **y**: Paired t-test. Variables with normal distribution are presented as mean ± standard deviation, while those without normal distribution are expressed as median (minimum–maximum).
Abbreviations: ALP, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **B12**, vitamin **B12**; BUN, blood urea nitrogen; **CRP**, C-reactive protein; **TIBC**, total iron-binding capacity; **GFR**, glomerular filtration rate; **GGT**, gamma-glutamyl transferase; **HALP**, hemoglobin, albumin, lymphocyte, and platelet score; **HCT**, hematocrit; **HGB**, hemoglobin; **PIV**, Pan-Immune-Inflammation Value; SII, Systemic Immune-Inflammation Index; **TS**, transferrin saturation.

 ISSN 0326-3428

Table 2: Comparison of Biochemical Changes (Pre–Post) According to Glomerular Filtration Rate

	<60	60 ve üzeri	Toplam	p
BUN (mg/dL)	9,63 (-115,56 - 107)	0 (-55,64 - 44,94)	0,13 (-115,56 - 107)	0,057
Creatinine (mg/dL)	0,05 (-2,76 - 1,28)	-0,01 (-1,31 - 0,44)	0 (-2,76 - 1,28)	0,374
Sodium (mEq/L)	-2,56 ± 5,06	-0,99 ± 3,63	-1,43 ± 4,13	0,097
Potasium (mEq/L)	-0,26 ± 0,93	-0,02 ± 0,48	-0,08 ± 0,65	0,147
Calcium (mg/dL)	-0,33 ± 0,67	-0,25 ± 0,76	-0,26 ± 0,74	0,610
Phosphorus (mg/dL)	0,17 ± 1,18	0,26 ± 1,02	0,23 ± 1,07	0,695
Albumin (g/L)	-0,09 ± 0,39	-0,1 ± 0,54	-0,1 ± 0,5	0,894
CRP (mg/L)	0,01 (-25,27 - 23,17)	0 (-14,26 - 11,61)	0 (-25,27 - 23,17)	0,927
AST (u/L)	4 (-16 - 26)	-2 (-79 - 67)	-1 (-79 - 67)	0,011
ALT (ıu/L)	-1,5 (-27 - 22)	-3 (-236 - 163)	-3 (-236 - 163)	0,383
ALP (ıu/L)	-8,5 (-58 - 129)	-3 (-43 - 314)	-3 (-81 - 314)	0,764
GGT (ıu/L)	-2,5 (-64 - 41)	-2 (-95 - 376)	-2 (-191 - 376)	0,875
Iron (mcg/dL)	-16 (-140 - 33)	-48,5 (-203 - 11)	-37 (-203 - 33)	<0,001
TIBC (mcg/dL)	55,36 ± 90,24	155,19 ± 85,74	129,07 ± 95,62	<0,001
Ferritin (ng/mL)	-153,1 (-787,1 - -4)	-117 (-504,7 - 0,1)	-119,05 (-787,1 - 0,1)	0,556
Folat (ng/mL)	3,6 (-19,04 - 12,73)	0,46 (-17,87 - 6,14)	0,87 (-19,04 - 12,73)	0,032
B12 (pg/mL)	-1,5 (-421 - 152)	-33 (-1753 - 146)	-19 (-1753 - 152)	0,707
HGB (g/dL)	-1,27 ± 1,07	-2,56 ± 1,86	-2,32 ± 1,8	<0,001
HCT (%)	-4,09 ± 3,59	-6,97 ± 5,4	-6,43 ± 5,22	<0,001
SII	124,77 (-2107,15 - 3553,72)	48,01 (-10379,14 - 1806,22)	54,86 (-10379,14 - 3553,72)	0,081
PIV	144,86 (-667,27 - 2350,2)	47,62 (-7787,27 - 3080,16)	59,68 (-7787,27 - 3080,16)	0,039
HALP	-0,05 (-0,42 - 0,24)	-0,08 (-0,65 - 1,8)	-0,08 (-0,65 - 1,8)	0,162

x: Mann–Whitney U test; **y**: Independent t-test.
Variables with normal distribution are presented as mean ± standard deviation, while those without normal distribution are expressed as median (minimum–maximum).
Abbreviations: **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **B12**, vitamin **B12**; **BUN**, blood urea nitrogen; **CRP**, C-reactive protein; **TIBC**, total iron-binding capacity; **GFR**, glomerular filtration rate; **GGT**, gamma-glutamyl transferase; **HALP**, hemoglobin, albumin, lymphocyte, and platelet score; **HCT**, hematocrit; **HGB**, hemoglobin; **PIV**, Pan-Immune-Inflammation Value; **SII**, Systemic Immune-Inflammation Index; **TS**, transferrin saturation.

DISCUSSION

In this study, intravenous ferric carboxymaltose therapy was shown not only to improve anemia-related parameters but also to induce significant changes in the indicators of inflammation and immunonutritional status, namely SII, PIV, and HALP scores. Our findings suggest that the response to FCM may vary with kidney function level, with more pronounced improvements in hematological parameters observed in patients with higher GFR values. Moreover, the observation that both 500 mg and 1000 mg doses yielded comparable results suggests that lower doses may also be effective. These novel findings extend beyond studies in the literature that have predominantly focused on hemoglobin and iron parameters, underscoring FCM's potential contribution to inflammatory and immunonutritional responses.

In our study, hemoglobin, ferritin, and transferrin saturation increased significantly following FCM treatment. These results are consistent with previous randomized controlled and observational studies conducted in both patients with chronic kidney disease and other

populations [19,22].

In our study, although increases in Hb and Hct levels were significant in both GFR groups, the magnitude of these increases was more pronounced in patients with GFR ≥60 ml/min/1.73 m² (Hb +2.56 vs. +1.27 g/dL; Hct +6.97 vs. +4.09%; both p<0.001). Similarly, the increase in serum iron was greater in the higher GFR group (+48.5 vs. +16 µg/dL, p<0.001), and the reduction in TIBC was also more marked (−155.1 vs. −55.3 µg/dL, p<0.001). These findings indicate that the hematological response to iron therapy is stronger in patients with better kidney function. In the literature, this phenomenon has been explained by elevated hepcidin levels in chronic kidney disease, which suppress intestinal iron absorption and limit the functional utilization of intravenous iron. Increased hepcidin concentrations have been shown to result from both heightened inflammation, which is central to the pathogenesis of chronic kidney disease, and, to some extent, decreased renal clearance associated with impaired kidney function [23]. These mechanisms may underlie the more limited increases in Hb, Hct, and serum iron, as well as the smaller reduction in TIBC, observed in the GFR <60 group.

In our study, a statistically significant increase in vitamin B12 levels (p=0.026) and a slight but not statistically significant decrease in folate levels (p=0.110) were observed following FCM treatment. Different results on this issue have been reported in the literature. For example, in a retrospective study of 202 women with iron-deficiency anemia in Türkiye, Açık and Aygün reported decreases in B12 and folate levels, accompanied by increases in hemoglobin and ferritin values, after iron therapy (oral and intravenous; 4–8 weeks of follow-up) [24]. Similarly, in the study by Erdem et al., oral ferrous glycine sulfate was compared with intravenous FCM, and the percentage decreases in vitamin B12 and folic acid were more pronounced in the intravenous FCM group (p=0.005 and p=0.001, respectively) [25]. These findings have been interpreted as increased erythropoiesis, leading to greater consumption of B12 and folate and thereby reducing serum levels. By contrast, Remacha et al. reported that oral iron therapy in young women affected not only hematological parameters but also various biochemical pathways, including B12, folate, and lipid metabolism, with these values returning to normal during treatment. Although the exact mechanism remains unclear, regulation of iron homeostasis and hepcidin-mediated processes have been suggested to contribute to this improvement [26]. Therefore, potential fluctuations in vitamin B12 and folate levels after IV FCM therapy should be considered, and monitoring these parameters during treatment may be beneficial.

In our study, a statistically significant but clinically modest increase in serum sodium levels was observed following FCM treatment (from 138 to 140 mmol/L; p<0.001). Although excipients such as sodium hydroxide are present in FCM formulations, their amounts are negligible relative to daily sodium intake and are not expected to affect serum sodium levels [27]. However, FCM administration is diluted with 0.9% sodium chloride (up to 250 mL), which corresponds to approximately 38 mEq of sodium and a short-term volume expansion; saline infusion has been shown in the literature to increase blood pressure, particularly in salt-sensitive hypertensive patients [28]. Furthermore, clinical studies have reported transient elevations in systolic blood pressure occurring in the post-dose period following FCM administration, which typically resolve within about 30 minutes [27]. In the randomized controlled trial by Qunibi et al. comparing intravenous FCM with oral iron therapy in non-dialysis CKD patients with iron deficiency anemia, hypertension was not among the prominent adverse events [20], whereas in the FIND-CKD trial by Macdougall et al., peripheral edema and hypertension were reported among the most common adverse events in both the oral iron and FCM groups [21]. These findings, together with the increase in sodium observed in our study, suggest that the effect may be driven more by the infusion vehicle and patient comorbidities than by the formulation itself. Nevertheless, close monitoring after administration may be beneficial, particularly in patients with hypertension or heart failure.

In our study, a statistically significant but clinically modest decrease in serum phosphorus levels was observed following FCM treatment

(3.6 → 3.4 mg/dL; p=0.015). Although this change does not meet the clinical definition of hypophosphatemia (<2.5 mg/dL), the literature reports that hypophosphatemia may be a significant concern following intravenous FCM administration, particularly with repeated doses and during long-term follow-up [29]. The proposed mechanism involves increased fibroblast growth factor 23 (FGF23) levels and enhanced renal phosphate excretion [30,31]. The small decline observed in our study appears consistent with single-dose administration and short follow-up. Nevertheless, closer monitoring may be warranted in patients receiving repeated doses, those with malnutrition, or those with low baseline phosphorus levels. In the group with GFR <60 ml/min/1.73 m², the relatively small sample size raises the possibility that insufficient statistical power contributed to the lack of significant findings in subgroup analyses. Therefore, larger prospective studies are needed to assess the long-term clinical implications of changes in phosphorus levels.

In our study, ALT levels increased from 15 to 18 U/L and GGT levels from 14 to 20 U/L following FCM administration (both p<0.001). Although these increases in group medians were small in magnitude and largely remained within the reference range at the group level, individual patients may have approached the upper limit. Due to the retrospective design, confounding factors such as concomitant hepatotoxic drug use, alcohol history, viral hepatitis, and underlying liver disease could not be systematically excluded; therefore, the observed changes in liver enzymes cannot be attributed solely to FCM. In the literature, studies comparing the effects of different iron preparations on liver enzymes have reported significant increases in AST, ALT, and alkaline phosphatase (ALP) levels in rats treated with high-molecular-weight (HMW) and low-molecular-weight (LMW) iron dextran or iron gluconate. By contrast, such increases were reported to be less pronounced with more stable preparations such as FCM [32]. The high molecular weight and thermodynamic stability of FCM ensure controlled iron release, preventing abrupt elevations in free ionic iron levels; this mechanism may, in turn, reduce the risk of oxidative stress and hepatotoxicity associated with free iron. Although FCM has been suggested to be safer than other iron preparations, monitoring of liver function after treatment remains important [32]. Further clinical data and long-term follow-up studies are needed to provide more conclusive evidence regarding the hepatic safety profile of FCM.

In recent years, immune-inflammatory indices have been shown to have prognostic value in many clinical conditions [8,10,16,33,34]. In our study, significant changes were observed in three different immune-inflammatory markers following intravenous FCM therapy. The SII decreased significantly from 731 before treatment to 615 after treatment (p=0.040). Similarly, PIV declined markedly from 384.1 to 324.6 (p<0.001). Conversely, the HALP score increased from 0.20 to 0.29 (p<0.001). These changes may indicate a reduction in systemic inflammatory burden and an improvement in immunonutritional status after treatment. In subgroup analyses, no significant differences in inflammatory indices were observed between GFR groups. Logistic regression analysis also showed that GFR was not independently associated with changes in HALP, SII, or PIV scores, suggesting that the inflammatory response may not be explained solely by kidney function. The relatively small sample size in the group with GFR <60 ml/min/1.73 m² may have reduced statistical power and limited the ability to detect potential associations.

Although concerns have been raised that intravenous iron therapies may increase inflammation, FCM has been suggested to exert a lower pro-inflammatory effect compared with other iron preparations due to its stable structure and pharmacokinetic properties [11].

The literature reports that FCM administration does not increase inflammation, a finding attributed to several mechanisms [12]. While some studies have proposed that correcting anemia may suppress the inflammatory response, no direct correlation between changes in hemoglobin and inflammatory parameters has been demonstrated.

Moreover, the high molecular weight and thermodynamic stability of FCM ensure controlled iron release and prevent abrupt increases in free ionic iron levels, thereby reducing transferrin oversaturation and the

inflammatory response associated with free iron, which may contribute to FCM's more favorable safety profile compared with other preparations. However, it has also been emphasized that data on long-term use are limited, and inflammatory effects may change over time [12].

In our study, no significant differences were observed between the dose groups (500 mg vs. 1000 mg) in terms of changes in HALP, SII, and PIV scores. The observation of similar favorable changes with both doses suggests that the improvements in these indices may not be solely attributable to iron replacement by FCM. It should also be considered that FCM may exhibit a "plateau effect" beyond a certain dose, indicating that lower doses could provide comparable efficacy. Therefore, individualized needs should be taken into account when selecting doses, and further confirmation through larger prospective studies is warranted.

Limitations

This study has several limitations. First, it was designed as a retrospective, single-center study. In particular, the relatively small number of patients with GFR <60 ml/min/1.73 m² limited the statistical power of subgroup analyses in this population. The FCM dosing regimen was not randomized but was determined based on clinicians' calculations of iron deficit. As a result, the approximately 70%/30% imbalance between dose groups restricted the power of subgroup comparisons. In addition, post-treatment laboratory data were limited to a short-term follow-up (week 2), preventing assessment of the long-term effects of FCM therapy on inflammatory parameters. Regarding changes in liver enzymes, data on potential confounding factors such as concomitant liver disease, hepatotoxic drug use, or alcohol consumption were not available.

CONCLUSIONS

In this study, intravenous FCM therapy was shown to exert significant effects not only on hematological parameters but also on inflammatory indices. In particular, the increase in the HALP score and the significant decreases in SII and PIV scores highlight the potential of FCM to suppress systemic inflammation while improving immunonutritional status.

The absence of significant differences between GFR and dose groups suggests that the treatment response may be more closely related to individual inflammatory profiles. Furthermore, our findings emphasize the need to monitor patients after treatment for fluctuations in vitamin B12 and folate, decreases in phosphorus, and increases in liver enzymes.

To better clarify the potential effects of FCM on inflammatory response and immunonutritional status, prospective, and long-term clinical studies are warranted, particularly those ensuring equal representation of patients with GFR <60 ml/min/1.73 m² and systematically accounting for confounding factors such as vitamin D status, obesity, infection, and smoking.

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