Effect of Ferric Citrate versus Ferrous Sulfate on Iron and Phosphate Parameters in Patients with Iron Deficiency and CKD

A Randomized Trial

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Abstract

Background and objectives Ferric citrate is an oral medication approved for treatment of iron deficiency anemia in patients with CKD not requiring dialysis. The relative efficacy of ferric citrate versus ferrous sulfate in treating iron deficiency in patients with CKD is unclear.

Design, setting, participants, & measurements We randomized 60 adults with moderate to severe CKD (eGFR 15–45 ml/min per 1.73 m^2) and iron deficiency (transferrin saturation [TSAT] ≤30% and ferritin ≤300 ng/ml) to ferric citrate (2 g three times a day with meals, n=30) or ferrous sulfate (325 mg three times a day, n=30) for 12 weeks. Primary outcomes were change in TSAT and ferritin from baseline to 12 weeks. Secondary outcomes were change in hemoglobin, fibroblast growth factor 23 (FGF23), and hepcidin.

Results Baseline characteristics were well balanced between study arms. There was a greater increase in TSAT (between-group difference in mean change, 8%; 95% confidence interval [95% CI], 1 to 15; P=0.02) and ferritin (between-group difference in mean change, 37 ng/ml; 95% CI, 10 to 64; P=0.009) from baseline to 12 weeks in participants randomized to ferric citrate as compared with ferrous sulfate. Similarly, as compared with ferrous sulfate, treatment with ferric citrate resulted in a greater increase in hepcidin from baseline to 12 weeks (between-group difference, 69 pg/ml; 95% CI, 8 to 130). There were no between-group differences in mean change for hemoglobin (0.3 g/dl; 95% CI, −0.2 to 0.8), intact FGF23 (−29 pg/ml; 95% CI, −59 to 0.1), or C-terminal FGF23 (61 RU/ml; 95% CI, −181 to 58). The incidence of adverse events did not differ between treatment arms.

Conclusions As compared with ferrous sulfate, treatment with ferric citrate for 12 weeks resulted in a greater mean increase in TSAT and ferritin concentrations in individuals with moderate to severe CKD and iron deficiency.

Clinical Trial registry name and registration number Impact of Ferric Citrate vs Ferrous Sulfate on Iron Parameters and Hemoglobin in Individuals With Moderate to Severe Chronic Kidney Disease (CKD) With Iron Deficiency, NCT02888171.

CJASN 15: 1251–1258, 2020. doi: https://doi.org/10.2215/CJN.15291219

Introduction

Iron deficiency anemia is a common complication of CKD (1). Ferric citrate is an oral medicine approved by the US Food and Drug Administration for the treatment of iron deficiency anemia in patients with CKD not requiring dialysis. This indication was granted on the basis of data showing that ferric citrate increased circulating iron concentrations and hemoglobin in patients with CKD with iron deficiency anemia as compared with placebo (2,3). However, it is unknown whether the effects of ferric citrate on serum iron parameters substantively differ from ferrous sulfate, the most frequently used oral iron supplement (4). This is important in that ferrous sulfate has been shown to be relatively efficacious in increasing iron concentrations and hemoglobin in individuals with CKD not requiring dialysis (5–8), and is available over the counter.

Aside from anemia, iron deficiency also results in high circulating fibroblast growth factor 23 (FGF23) by inducing the synthesis and cleavage of FGF23 (9,10). Consistent with this, intravenous iron reduces C-terminal fibroblast growth factor 23 (cFGF23) in individuals with iron deficient anemia (11), but the effects of oral iron supplements on FGF23 are less clear, particularly in patients with CKD. This may be important given experimental data showing that elevated FGF23 adversely affects cardiac structure and function in animals with CKD. Notably, ferric citrate was originally approved as an oral phosphate

binder for the treatment of hyperphosphatemia in patients with ESKD, and decreases circulating FGF23 concentrations in patients with CKD not requiring dialysis (2,3). However, it is unclear whether ferric citrate more effectively reduces FGF23 in patients with CKD by both increasing circulating iron and restricting phosphate absorption as compared with ferrous sulfate, which increases iron alone. Accordingly, we conducted an investigator-initiated, randomized trial to examine the effects of oral ferric citrate versus ferrous sulfate on iron parameters, hemoglobin, and FGF23 in iron-deficient patients with CKD.

Materials and Methods

Study Setting and Population

From September 2016 to October 2018, we conducted an investigator-initiated, randomized, open-label study of 60 participants with CKD. Financial support was provided as an independent research grant by Keryx Biopharmaceuticals, Inc., a wholly-owned subsidiary of Akebia Therapeutics, Inc. The study was approved (F160318006) by the University of Alabama at Birmingham (UAB) Institutional Review Board for Human Use, and all participants provided written informed consent. This study complied with Clinicaltrials.gov registration requirements (registration number NCT02888171).

Participants were recruited from the nephrology outpatient clinics at UAB. Inclusion criteria included being ≥18 years of age, having an eGFR 15–45 ml/min per 1.73 m^2, and having a transferrin saturation (TSAT) ≤30% and a ferritin ≤300 ng/ml (2). Exclusion criteria included hemoglobin concentrations >13 g/dl (which was changed from >11 g/dl in the original protocol to enhance recruitment of men); severe anemia, defined as hemoglobin <8.0 g/dl in men and <7.0 g/dl in women; a known disorder of iron homeostasis; known cause of anemia other than iron deficiency or kidney disease; irritable bowel disease or inflammatory bowel disease; cirrhosis or the presence of alanine aminotransferase, aspartate aminotransferase, or bilirubin concentrations three times above the normal range; serum phosphate <3.0 mg/dl; symptomatic gastrointestinal bleeding within 12 weeks before the screening visit; receipt of any form of kidney replacement therapy; pregnancy or lactation in women; currently receiving nutritional vitamin D in dosages >2000 IU/d; receipt of any erythropoesis-stimulating agent within 4 weeks of the screening visit; receipt of any intravenous iron agent within 8 weeks of screening; receipt of a blood transfusion within 4 weeks of screening; known allergies or severe adverse reactions to prior oral iron therapy; current use of oral phosphate binders; and current use of calcitriol or any other activated vitamin D analog. Participants who were taking oral iron supplements at the time of the screening visit were allowed to participate but had to undergo a washout period of at least 4 weeks before randomization.

Study Protocol and Intervention

All study visits occurred on the Clinical Research Unit of the Center for Clinical and Translational Science at UAB. Participants were randomized 1:1 to receive either oral ferric citrate (2 g by mouth three times a day with meals, equivalent to 1260 mg of elemental iron per day) or ferrous sulfate (325 mg by mouth three times a day, equivalent to 195 mg of elemental iron per day) for a period of 12 weeks (Supplemental Figure 1). Randomization was accomplished by study staff using a computer-generated randomization code with permuted blocks (block size of 4–6), stratified by presence or absence of severe iron deficiency (defined as a TSAT ≤20% and a ferritin ≤100 ng/ml). Blood was obtained at baseline and at weeks 2, 6, and 12 to assess the effect of ferric citrate versus ferrous sulfate on primary and secondary outcome variables. Adherence to randomized medication assignment was assessed as the proportion of participants who took at least two thirds of the study medication, as determined by manually counting pills left in study medication bottles brought to each follow-up visit.

Outcomes of Interest

The primary estimand was the change in TSAT and serum ferritin from baseline to the end of treatment. Measurements of TSAT and ferritin were done using standard assays in the main UAB hospital laboratory. Secondary estimands included the change in hemoglobin, FGF23, and hepcidin. Hemoglobin measurements were done in the main UAB hospital laboratory using standard equipment. Both intact fibroblast growth factor 23 (iFGF23) and cFGF23 were measured in duplicate in plasma samples in the UAB Metabolism Core Laboratory/Human Physiology Core Laboratory using established ELISAs (Quidel, San Clemente, CA), with coefficients of variation (CVs) <5%. Quantitative measurements of bioactive 25-hepcidin were obtained in sera using a competitive ELISA (Intrinsic LifeSciences, La Jolla, CA) (12). The intra-assay CVs of hepcidin were 11%–19% in the lower range of hepcidin values (<30 ng/ml) and 4%–11% in the upper range of hepcidin values (>30 ng/ml), and the corresponding interassay CVs were 12%–40% in the lower range of hepcidin values and 2%–10% in the higher range. In addition, erythroferrone concentrations were measured in serum samples as a *post hoc* exploratory analysis using an established ELISA (Intrinsic LifeSciences), with CVs <15%. Because of the expense of measurement, hepcidin and erythroferrone were measured in a subset of participants (the first 40 individuals who completed the study, 20 randomized to both ferric citrate and ferrous sulfate) at three time points (baseline, 2 weeks, and 12 weeks). In exploratory *post hoc* analyses, intact parathyroid hormone concentrations were measured in serum samples from each visit using an established ELISA (Quidel) and inflammatory cytokines (IFN-γ, IL-10, IL-17A, IL-1β, IL-6, TNF-α, IL-17E/IL-25, IL-17F, IL-21, and IL22) were measured in serum samples at each visit using electrochemiluminescence assays (U-PLEX TH17 Combo 2; Meso Scale Discovery, Rockville, MD).

Statistical Analyses

Using a modified intention-to-treat analysis, all participants who were randomized, received at least one dose of study drug, and attended at least one postbaseline visit were included in the analysis. We used linear mixed-effects models to compare primary and secondary efficacy end points by randomization group, using compound symmetry to account for repeated measures within each participant.

In these models, randomized group, time, and group×time terms were analyzed as fixed effects, and participants were analyzed as random effects. The primary outcome was the difference in the mean change in each outcome variable from baseline to 12 weeks. We also examined differences in the rate of change in each analyte across all time points by testing the statistical significance of group×time interaction terms in the model. In these latter models, when there was a significant effect of time, we localized individually significant changes in postbaseline time points by comparing with baseline values in the mixed linear models. We natural log-transformed FGF23 concentrations to achieve a normal distribution. The proportion of participants who experienced an adverse event at any time after the baseline visit were compared by randomization group using the Fisher exact test. Two-tailed P values <0.05 were prespecified as statistically significant. All analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC).

Sample Size Calculation

The sample size estimation was powered to detect a significant difference in the mean change in TSAT and ferritin in response to oral ferric citrate versus ferrous sulfate challenge. In a prior study, treatment with ferric citrate for 12 weeks raised serum ferritin by 67% as compared with placebo (2). To detect a more modest 40% difference in the rise of ferritin in individuals taking ferrous sulfate versus ferric citrate over a similar period of intervention, we would need to recruit 48 individuals overall (24 per arm), assuming a type 1 error of 0.05 and a power of 80%. To account for 20% dropout, we aimed to recruit a total of 60 participants. We estimated that this would provide 80% power to detect at least a 20% difference in the change in TSAT between treatment groups. For these estimates, we assumed that ferritin and TSAT were normally distributed and that the difference in their mean change over time would be normally distributed.

Results

Study Population

Participant disposition is shown in Figure 1. Of the 60 individuals randomized, nine withdrew before the final visit ($n=5$ for ferric citrate and $n=4$ for ferrous sulfate) for the reasons listed in Figure 1, leaving a total of 51 participants who completed all study visits ($n=25$ for ferric citrate and $n=26$ for ferrous sulfate). A total of 57 participants ($n=28$ for ferric citrate and $n=29$ for ferrous sulfate) were randomized, received the study drug, and completed at least one postbaseline visit, and were included in the modified intention-to-treat analysis. Baseline characteristics of study participants by randomization assignment are depicted in Table 1. Participants were well balanced except for baseline FGF23 concentrations, which were higher in participants randomized to ferrous sulfate as compared with ferric citrate. On average, participants randomized to ferric citrate took 5.2 tablets per day (approximately 1 g of elemental iron per day), whereas participants randomized to ferrous sulfate took 2.9 tablets per day (190 mg of elemental iron per day). Adherence was high in both arms, with participants randomized to ferric citrate taking 85% of the assigned drug and participants taking ferrous sulfate taking 92% of the assigned study drug.

Primary Outcomes

Baseline and mean changes in TSAT and ferritin after 12 weeks are depicted in Table 2. Mean TSAT increased by 8% in those randomized to ferric citrate (95% confidence interval [95% CI], 1 to 14), but did not change in those randomized to ferrous sulfate (mean change, −1%; 95% CI, −3 to 2), with a statistically significant between-group difference in the mean change from baseline to 12 weeks (8%; 95% CI, 1 to 15; $P_{\text{interaction}}=0.02$). Similarly, serum ferritin concentrations increased in those randomized to ferric citrate (mean change, 49 ng/ml; 95% CI, 26 to 73), but not those randomized to ferrous sulfate (mean change,

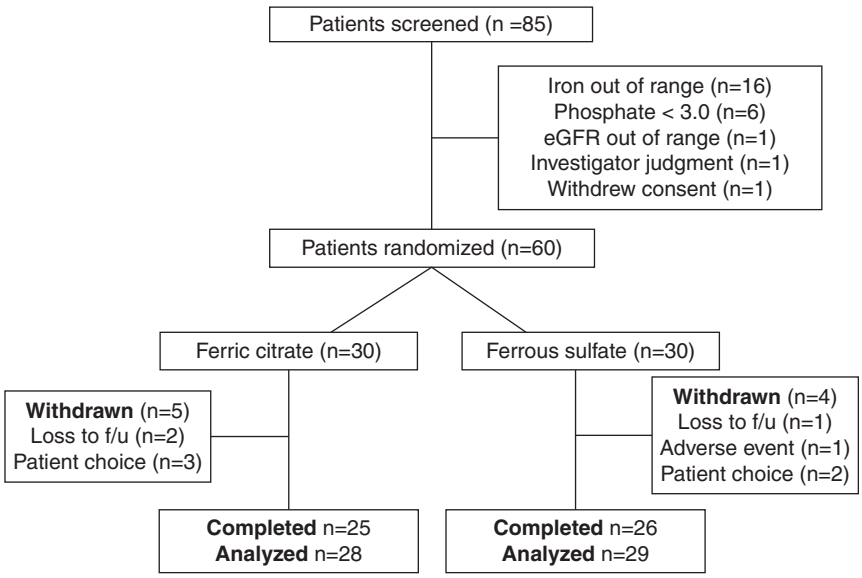

Figure 1. | **Study flow diagram**.

Table 1. Baseline characteristics of the study sample by randomization arm

Characteristic	Ferric Citrate	Ferrous Sulfate
N	30	30
Age, yr	60±12	63±11
Men, *n* (%)	10 (33)	11 (37)
Black race, *n* (%)	16 (53)	17 (57)
Body mass index, kg/m^2	37±8	36±9
Systolic BP, mm Hg	136±21	134±20
Diastolic BP, mm Hg	74±11	73±10
Comorbidities, *n* (%)		
Diabetes	16 (57)	18 (62)
Hypertension	30 (100)	28 (93)
Coronary artery disease	4 (15)	3 (10)
Heart failure	3 (11)	6 (21)
Stroke	3 (10)	3 (10)
Dyslipidemia	15 (54)	19 (65)
COPD	2 (6)	2 (6)
Attributed cause of CKD, *n* (%)		
Diabetes	15 (50)	17 (57)
Hypertension	5 (17)	4 (13)
GN	2 (7)	1 (3)
PKD	2 (7)	3 (10)
Other	4 (13)	3 (10)
Unknown	2 (7)	2 (7)
Medication use, *n* (%)		
Aspirin	10 (33)	19 (63)
Statin	17 (57)	22 (73)
β-Blocker	20 (67)	19 (63)
ACE inhibitor	10 (33)	7 (23)
ARB	12 (40)	10 (34)
Oral iron	7 (23)	6 (20)
Laboratory values		
Phosphate, mg/dl	3.7±0.5	3.9±0.8
Calcium, mg/dl	9.3±0.4	9.3±0.7
eGFR, ml/min per 1.73 m^2	33±12	26±14
TSAT, %	18±6	19±6
Ferritin, ng/ml	90±70	100±59
Hemoglobin, g/dl	11.4±1.0	11.0±1.0
iFGF23, pg/ml	92 [65–120]	160 [97–241]
cFGF23, RU/ml	179 [130–242]	278 [181–526]
PTH, pg/ml	136±80	153±93

Values are depicted as proportions (*n*, %), mean (SD), or median [interquartile range]. COPD, chronic obstructive pulmonary disease; PKD, polycystic kidney disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; TSAT, transferrin saturation; iFGF23, intact fibroblast growth factor 23; cFGF23, C-terminal fibroblast growth factor 23; PTH, parathyroid hormone.

12 ng/ml; 95% CI, −4 to 28), with a statistically significant between-group difference in the mean change (37 ng/ml; 95% CI, 10 to 64; $P_{\text{interaction}}=0.009$). The results were similar in analyses examining differences in the rate of change over time across all time points (Figure 2), although the group×time interaction term was not statistically significant for TSAT ($P_{interaction}=0.16$). The results did not differ in sensitivity analyses adjusting for baseline eGFR.

Secondary Outcomes

There were no significant between-group differences in the mean change in hemoglobin (0.3 g/dl; 95% CI, −0.2 to 0.8; $P_{\text{interaction}}=0.19$), iFGF23 (−29 pg/ml; 95% CI, −59 to 0.1; $P_{\text{interaction}}=0.05$), or cFGF23 (61 RU/ml; 95% CI, −58 to 181; $P_{\text{interaction}}=0.31$) from baseline to 12 weeks (Table 2). The between-group difference in mean 12-week change in hepcidin was statistically significant (69 pg/ml; 95% CI, 8 to 130; $P_{\text{interaction}}=0.03$), with hepcidin concentrations significantly increasing in participants randomized to ferric citrate (mean change, 90 pg/ml; 95% CI, 30 to 150), but not those randomized to ferrous sulfate (mean change, 21 pg/ml; 95% CI, −8 to 4).

Exploratory Outcomes

There were no statistically significant between-group differences in the mean change in parathyroid hormone (7 pg/ml; 95% CI, −20 to 34; $P_{\text{interaction}}=0.62$), erythroferrone (0.0 pg/ml; 95% CI, −1.1 to 1.1; $P_{\text{interaction}}=0.98$), or any of the inflammatory cytokines from baseline to 12 weeks, as depicted in Supplemental Table 1.

Safety Parameters

There was no significant change in serum phosphate concentrations in either treatment group over the course of the study (Supplemental Table 1). Table 3 depicts adverse event rates that occurred with a frequency >10% in either

Table 2. Changes in iron parameters, hemoglobin, fibroblast growth factor 23, and hepcidin after 12 weeks of ferric citrate versus ferrous sulfate

Variable	Baseline Values, Mean (SD)		12-Wk Change from Baseline, Mean Estimate (95% CI)			
	Ferrous Sulfate	Ferric Citrate	Ferrous Sulfate	Ferric Citrate	Difference	*P* Value
Primary outcomes						
TSAT, %	21 (7)	19 (7)	−1 (−3 to 2)	8 (1 to 14)	8 (1 to 15)	0.02
Ferritin, ng/ml	104 (63)	87 (61)	12 (−4 to 28)	49 (26 to 73)	37 (10 to 64)	0.009
Secondary outcomes						
Hemoglobin, g/dl	11.0 (1.1)	11.4 (1.1)	0.0 (−0.3 to 0.4)	0.3 (0.1 to 0.5)	0.3 (−0.1 to 0.2)	0.19
iFGF23, pg/ml	178 (102)	160 (290)	−7 (−22 to 8)	−37 (−74 to 0)	−29 (−59 to 0.1)	0.05
cFGF23, RU/ml	437 (510)	291 (353)	−104 (−219 to 11)	−45 (−92 to 1)	61 (−58 to 181)	0.31
Hepcidin, pg/ml	87 (48)	82 (61)	21 (−8 to 49)	90 (30 to 150)	69 (8 to 130)	0.03

95% CI, 95% confidence interval; TSAT, transferrin saturation; iFGF23, intact fibroblast growth factor 23; cFGF23, C-terminal fibroblast growth factor 23.

treatment arm. In general, the study drugs were well tolerated, with gastrointestinal complaints being the most common adverse events. One participant in the ferrous sulfate group had to stop study drug because of dyspepsia. No participants had to stop study medication because of hypophosphatemia (serum phosphate ≤2.0 mg/dl). There were no serious adverse events or deaths during the trial period.

Discussion

In this study of individuals with CKD and iron deficiency, 12 weeks of treatment with ferric citrate resulted in greater increases in TSAT and serum ferritin than ferrous sulfate. Ferric citrate also increased hepcidin concentrations more than ferrous sulfate, whereas there were no between-group differences in the 12-week change in hemoglobin, iFGF23, or cFGF23.

Individuals with CKD have high circulating concentrations of hepcidin, resulting in reduced iron absorption in the gut (13–15). Using oral iron supplementation at high doses to overcome this block often causes gastrointestinal side effects, limiting the total quantity of elemental iron that can be delivered *via* the gastrointestinal tract with standard formulations. Each 1 g tablet of ferric citrate contains 210 mg of elemental iron, which could potentially allow for a greater total quantity of iron delivery than ferrous sulfate (65 mg of elemental iron per tablet) without resulting in more adverse effects. However, the relative efficacy of ferric citrate versus ferrous sulfate has not previously been examined.

We found that TSAT and serum ferritin concentrations significantly increased from baseline to 12 weeks in participants randomized to ferric citrate but not those randomized to ferrous sulfate. These findings add to the current literature by showing that oral ferric citrate not only

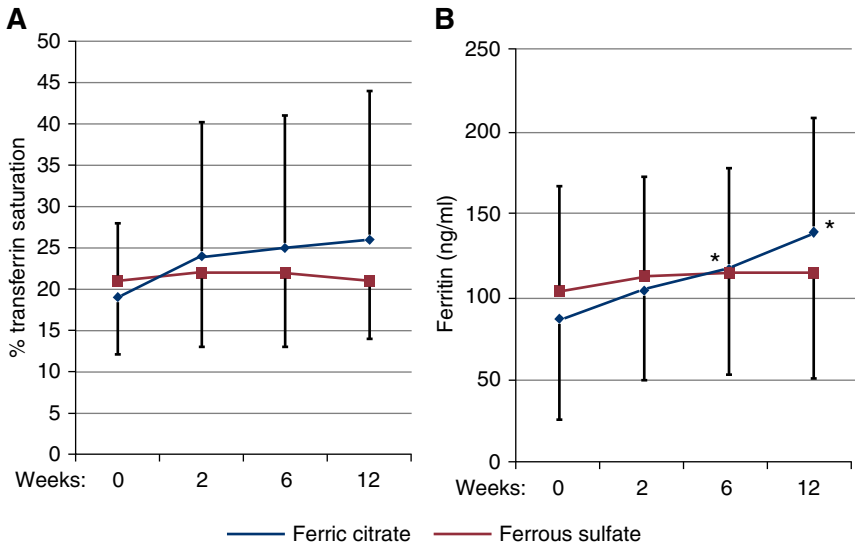

Figure 2. | Percent transferrin saturation and ferritin concentrations increased in those randomized to ferric citrate but not those randomized to ferrous sulfate over 12 weeks. Transferrin saturation (TSAT) (A) and ferritin (B). Results shown as mean±SD. Asterisks denote statistically significant difference from the baseline value. The *P* values for the group×time interaction terms for TSAT and ferritin were 0.14 and <0.001, respectively.

Table 3. Number (proportion) of adverse events by randomization arm (reported in 10% or more in either group)

Adverse Event	Ferric Citrate, *n* (%)	Ferrous Sulfate, *n* (%)
Total *N*	30	30
Weight loss	3 (10)	7 (24)
Weight gain	5 (17)	8 (27)
Fatigue	6 (20)	3 (10)
Infection	5 (17)	1 (4)
Eye pain	2 (7)	5 (17)
Vision changes	4 (14)	1 (4)
Nasal congestion	3 (10)	4 (14)
Shortness of breath	2 (7)	5 (16)
Cough	3 (10)	1 (4)
Nausea	6 (20)	5 (16)
Diarrhea	9 (30)	5 (16)
Constipation	9 (30)	11 (36)
Change in stool color	16 (53)	8 (27)
Anorexia	2 (7)	8 (27)
GERD	3 (10)	1 (4)
Frequency	2 (7)	5 (16)
Muscle pain	3 (10)	2 (7)
Edema	0	4 (14)
Headache	2 (7)	6 (20)
Change smell/taste	3 (10)	2 (7)

GERD, gastroesophageal reflux disease.

increases circulating TSAT and ferritin in patients with CKD (2,3), but it appears to do so more effectively than ferrous sulfate, the most commonly used oral iron supplement. The clinical implications of these findings are less clear. Although hemoglobin significantly increased in those randomized to ferric citrate, but not those randomized to ferrous sulfate, the between-group difference was not statistically significant. Larger studies are needed to determine whether ferric citrate more effectively raises hemoglobin in individuals with iron deficiency anemia than ferrous sulfate, which, if so, may help inform decisions on the initial oral agent to treat iron deficient anemia in CKD.

We examined several secondary outcomes as well. Experimental data have shown that iron deficiency increases FGF23 expression by stabilizing hypoxia-inducible factor 1α, which in turn binds to a site in the *Fgf23* promoter to induce transcription (10,16). Prior studies in individuals with iron deficiency have shown that intravenous iron infusion markedly decreased cFGF23 concentrations but had a more negligible effect on iFGF23 concentrations (11). The effects of oral iron agents on FGF23 have been studied in less detail. Studies have shown that ferric citrate lowers circulating FGF23, likely by reducing dietary phosphate absorption (2,3), but no studies compared the effects of ferric citrate to ferrous sulfate. We did not find a between-group difference in the 12-week change of either iFGF23 or cFGF23 by treatment arm. Nonetheless, it is notable that the decrease in iFGF23 was numerically greater in those randomized to ferric citrate versus ferrous sulfate, and the between-group difference just missed statistical significance. Whether ferric citrate more effectively reduces iFGF23 than ferrous sulfate remains to be tested in an adequately powered study.

Despite the well known effect of oral iron on stimulating hepcidin secretion in healthy individuals (17–19), to our knowledge, only one prior study examined the effect of oral iron on hepcidin in patients with CKD (20). We observed that the changes in hepcidin mirrored those of TSAT and ferritin in that ferric citrate significantly increased serum hepcidin concentrations, whereas no significant effect was noted for ferrous sulfate. Anemia is a powerful stimulus for erythroferrone, which inhibits hepcidin expression in order to aid iron availability and, by extension, erythropoiesis (21). Despite the increase in hemoglobin in participants randomized to ferric citrate, we saw no significant change in erythroferrone.

Our study had important limitations. The sample size was relatively small and the length of treatment was only 12 weeks, precluding our ability to detect more modest effects on key outcome variables that may have been observed over a longer period of time. The iron parameters used for inclusion in the study were chosen to be comparable with what has been done in prior studies (2,3). However, it is possible that this may have resulted in the inclusion of individuals with very minor degrees of iron deficiency. Similarly, our entry criteria for hemoglobin may have allowed individuals with relatively minor anemia to be enrolled, making it more challenging to demonstrate an effect of iron supplementation on hemoglobin. It may have been preferable to have a longer wash-out period for individuals taking oral iron at the time of study entry. Despite randomization, there were differences in baseline characteristics between the two groups, specifically in FGF23 concentrations, which were higher in those randomized to ferrous sulfate versus ferric citrate. This was an open-label study, so participants and investigators were not blinded to the study drug. Nonetheless, the measurement of biochemical parameters partly mitigates any effects of the lack of blinding on assessment of end points. Finally, it is not clear that a greater increase in iron parameters in those randomized to ferric citrate justifies the cost when compared with ferrous sulfate. Studies examining hard end

points, such as the need for erythropoiesis-simulating agents to treat anemia, cardiovascular events, or hospitalization, would be needed to adequately assess this.

In summary, treatment with ferric citrate for 12 weeks resulted in a greater increase in TSAT and ferritin concentrations than ferrous sulfate in individuals with moderate to severe CKD and iron deficiency without any differences in adverse event profile. Further studies are needed to determine whether treatment with ferric citrate is more effective in treating iron deficiency anemia and related complications than ferrous sulfate in patients with CKD.

Disclosures

O.M. Gutiérrez reports receiving consulting fees from Akebia Therapeutics, grant support and consulting fees from Amgen, grant support from GSK, and consulting fees from QED Therapeutics. All remaining authors have nothing to disclose.

Funding

Financial support for this study was provided as an independent research grant by Keryx Biopharmaceuticals, Inc., now a wholly owned subsidiary of Akebia Therapeutics, Inc. Research supported in this publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), under award number UL1TR003096, and the National Institute Of Diabetes And Digestive And Kidney Diseases, NIH, under award numbers P30DK079626 and P30DK056336, and grant number K24DK116180.

Acknowledgments

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Because Dr. Orlando M. Gutiérrez is an Associate Editor of *CJASN*, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

Data Sharing Statement

The study authors are open to sharing deidentified data related to baseline participant characteristics and primary and secondary outcomes, as well as the study protocol and statistical analysis plan. Data will become available 1 year after online publication of the study, and only after appropriate institutional review board and data use agreements have been completed for sharing data.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.15291219/-/DCSupplemental.

Supplemental Figure 1. Study schema.

Supplemental Table 1. Changes in exploratory and safety outcome measures in those randomized to ferric citrate versus ferrous sulfate for 12 weeks.

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Received: December 14, 2019 **Accepted:** June 22, 2020

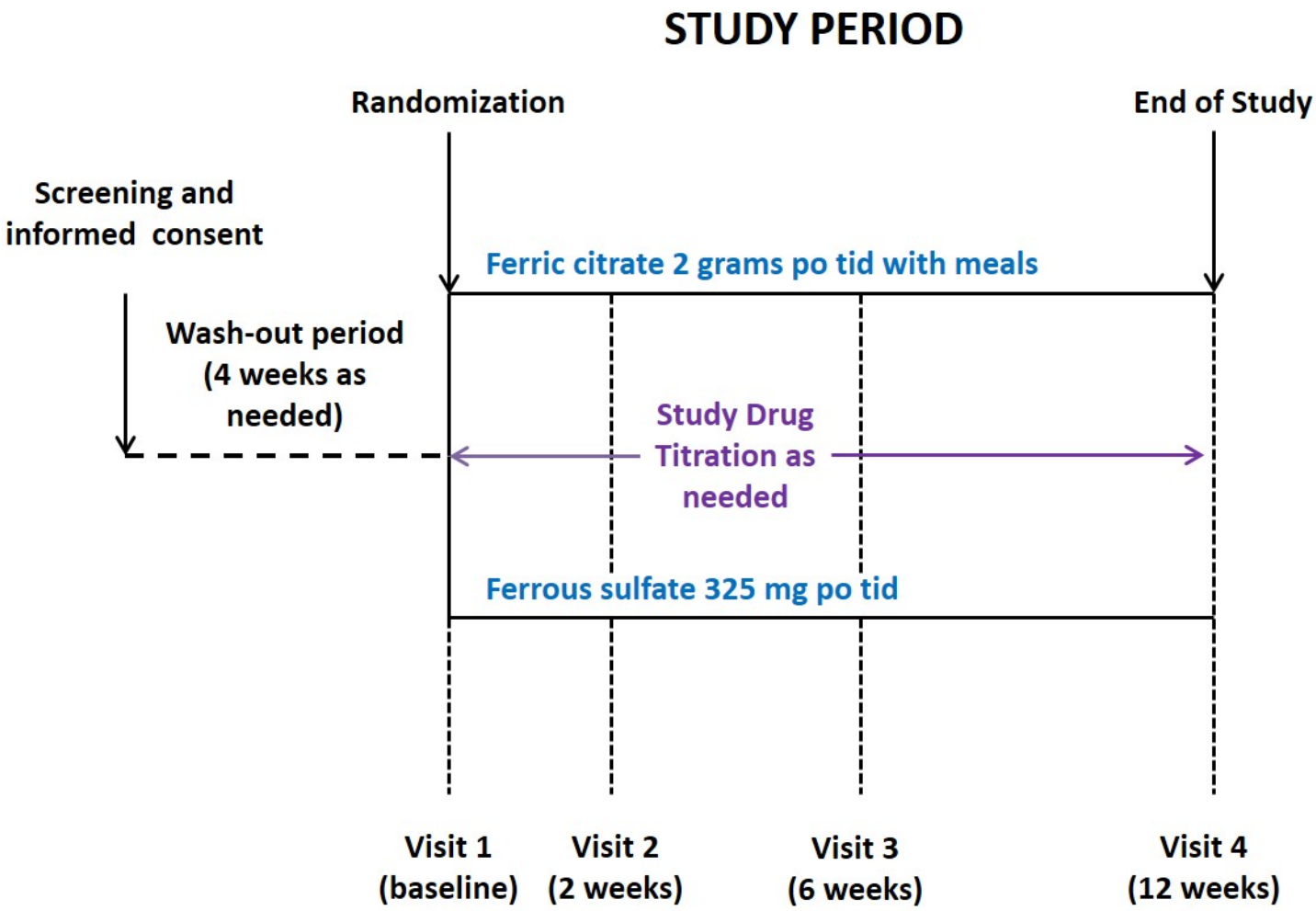
Published online ahead of print. Publication date available at www.cjasn.org.

SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Study schema.

Supplemental Table 1. Changes in exploratory and safety outcome measures in those randomized to ferric citrate vs. ferrous sulfate for 12 weeks.

Supplemental Figure. Study schema



Supplemental Table 1. Changes in exploratory and safety outcome measures in those randomized to ferric citrate vs. ferrous sulfate for 12 weeks.

	Baseline values, mean (SD)		**12-week change from baseline, mean estimate (95% CI)**			
	Ferrous sulfate	**Ferric citrate**	**Ferrous sulfate**	**Ferric citrate**	**Difference**	***P-value***
PTH, pg/ml	135 (81)	129 (69)	1 (-24,25)	-5 (-19,10)	7 (-20,34)	0.62
Phosphorus, mg/dL	4.0 (0.9)	3.7 (0.5)	-0.0 (-0.3,0.2)	-0.1 (-0.4,0.1)	-0.1 (-0.2,0.4)	0.52
ERFE, pg/ml	1.4 (0.4)	0.9 (1.4)	-0.3 (-0.9,0.2)	-0.3 (-1.4,0.8)	0.0 (-1.1,1.1)	0.98
IL-6, pg/ml	2.4 (1.9)	1.7 (1.0)	-0.0 (-0.4,0.4)	1.2 (-0.1,2.5)	1.2 (-0.2, 2.6)	0.08
IFN, pg/ml	33 (67)	14 (7)	-18 (-48,12)	7 (-4,18)	25 (-5,54)	0.10
IL-10, pg/ml	0.4 (0.3)	0.3 (0.3)	0.0 (-0.1,0.1)	0.1 (-0.0,0.2)	0.1 (-0.1,0.3)	0.27
TNF, pg/ml	3.1 (1.0)	2.6 (0.8)	-0.1 (-0.4,0.1)	0.1 (-0.2,0.4)	0.2 (-0.2,0.6)	0.23
IL-22, pg/ml	1.2 (1.2)	0.7 (0.7)	1.2 (-0.5,2.9)	0.1 (-0.4,0.6)	-1.0 (-2.7,0.6)	0.19

Abbreviations: PTH, parathyroid hormone; ERFE, erythroferrone; IL, interleukin; IFN, interferon-γ; TNF, tumor necrosis factor-α