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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the sup-
porting information tab for this article.

Hemoglobin response to ferric citrate in patients with nondialysis-dependent chronic kidney disease and iron deficiency anemia

To the Editor:

Anemia is a common complication in patients with chronic kidney dis-
ease (CKD) and often occurs due to iron deficiency. Causes of iron
deficiency in CKD include upregulation of hepcidin (a peptide hormone
that reduces iron transport across enterocytes) leading to decreased
dietary iron absorption, impaired iron release from body stores associ-
ated with heightened inflammation, and gastrointestinal blood loss. All
result in insufficient bone marrow iron availability and inefficient eryth-
ropoiesis, leading to iron deficiency anemia.[1]

Recent clinical practice guidelines from *Kidney Disease: Improving
Global Outcomes* recommend using oral or intravenous iron before
erythropoietin-stimulating agents for the treatment of iron deficiency
anemia in patients with nondialysis-dependent (NDD)-CKD.[1] Oral iron
preparations are typically ineffective and/or poorly tolerated due to
gastrointestinal side effects.[1] Intravenous iron is used infrequently in
nephrology offices as it requires intravenous infusion in a monitored
setting with facilities for resuscitation because of risks of serious
adverse drug events, including hypersensitivity reactions.[1]

In a randomized placebo-controlled trial of ferric citrate in 234
patients with NDD-CKD and iron deficiency anemia,[2] ferric citrate-
treated patients were significantly more likely to achieve a ≥ 1.0 g/dL
increase in hemoglobin (52.1% vs. 19.1% with placebo; $P < .001$) during
the 16-week randomized phase; the least-squares mean (LSM) relative
change in hemoglobin was 0.84 g/dL (95% confidence interval [CI],
0.58-1.10).[2]

The current analysis examined associations of baseline demographic, clinical, and laboratory variables with change in hemoglobin. It was hypothesized that patients with biochemical evidence of more severe iron deficiency would experience a more pronounced hemoglobin response.

Adult patients with iron deficiency anemia (hemoglobin 9.0–11.5 g/dL; transferrin saturation [TSAT] $\leq$ 25%; ferritin $\leq$ 200 ng/mL) and NDD-CKD (estimated glomerular filtration rate <60 mL/min/1.73 m^2) were included in the trial. Full clinical trial details are described elsewhere.[2] Here, multivariable linear regression analysis was used to identify variables associated with change in hemoglobin from baseline to week 16. Candidate variables were included in models based on forward selection and backward elimination using the Akaike information criterion (AIC). Treatment (ferric citrate vs. placebo) and baseline hemoglobin were fixed in all models. Potential interactions between treatment and each baseline variable were tested sequentially using stepwise AIC. For baseline variables with retained treatment interaction terms, mixed-effect models for repeated measures were fitted to confirm treatment interactions using all available longitudinal data and to assess the magnitude of treatment differences by baseline covariate levels (estimated at 25th and 75th percentiles). Two-tailed P-values <.05 were considered statistically significant. See Supporting Information Material for further detail.

Overall, 234 patients were randomized to receive ferric citrate ($n = 117$) or placebo ($n = 117$). This post hoc analysis employed the intention-to-treat population (ferric citrate, $n = 117$; placebo, $n = 115$), and baseline characteristics were similar across groups (Supporting Information Table S1).[2]

Among ferric citrate-treated patients, observed mean hemoglobin (standard deviation) increased from 10.4 g/dL (0.7) at baseline to 11.4 g/dL (1.1) at week 16.

The following variables were significantly associated with greater hemoglobin increases from baseline at 16 weeks: ferric citrate treatment ($P < .0001$), lower baseline hemoglobin ($P = .0160$), higher serum albumin ($P = .0007$), lower intact fibroblast growth factor 23 (FGF23; $P = .0024$), and lower TSAT ($P = .0189$) (Supporting Information Table S2; Sensitivity Analyses). Treatment interactions were retained for TSAT and ferritin only.

The treatment effect of ferric citrate versus placebo on hemoglobin was greater among patients with lower baseline TSAT than those with higher baseline TSAT. The estimated LSM difference at 16 weeks was 1.16 g/dL (95% CI, 0.84-1.48; $P < .0001$) at TSAT 15% and 0.78 g/dL (95% CI, 0.48-1.08; $P < .0001$) at TSAT 24% (treatment $\times$ baseline TSAT $\times$ week 16 interaction $P = .0426$). Ferric citrate-treated patients with lower versus higher baseline TSAT showed a greater rate of hemoglobin rise (Figure 1A).

Similarly, the treatment effect of ferric citrate versus placebo was greater among patients with lower baseline ferritin (estimated LSM difference at ferritin 35 ng/mL, 1.12 g/dL; 95% CI, 0.78-1.45; $P < .0001$) than patients with higher baseline ferritin (estimated LSM difference at ferritin 126 ng/mL, 0.79 g/dL; 95% CI, 0.46-1.12; $P < .0001$; treatment $\times$ baseline ferritin $\times$ week 16 interaction, $P = .0974$). Ferric citrate-treated patients with lower versus higher baseline ferritin showed a greater rate of hemoglobin rise (Figure 1B).
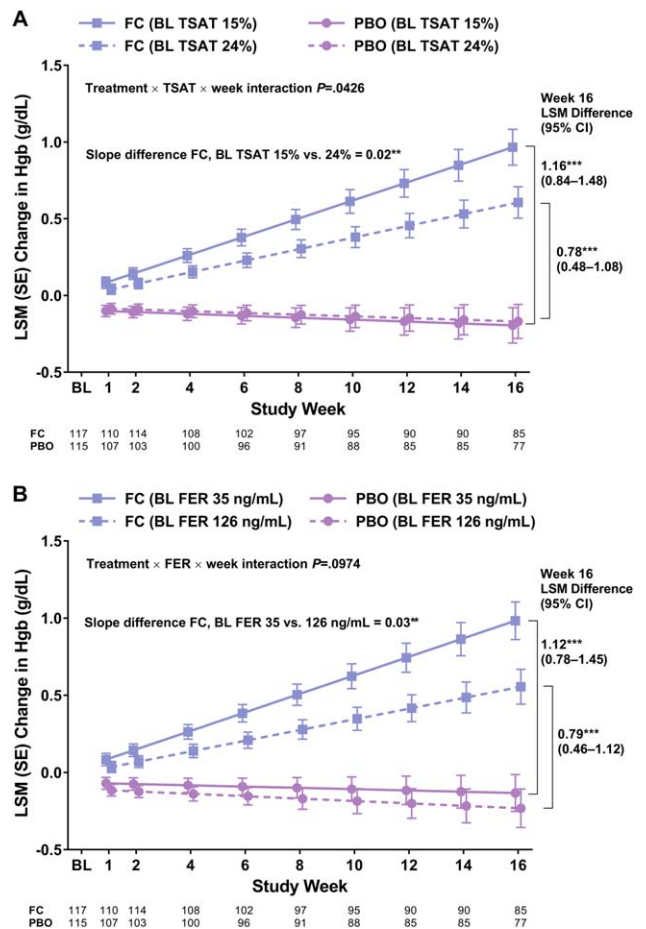

FIGURE 1 Mean trajectories of change in hemoglobin (Hgb) over 16 weeks by treatment (ferric citrate vs. PBO) estimated at (A) baseline (BL) TSAT level (15% vs. 24%) and (B) BL ferritin level (35 vs. 126 ng/mL). For panel A, data are adjusted LSM (SE) change from BL derived from an MMRM analysis with terms for treatment (ferric citrate vs. PBO), BL albumin, BL log iFGF23, BL TSAT, week, treatment $\times$ week interaction, treatment $\times$ TSAT interaction, and treatment $\times$ week $\times$ TSAT interaction as fixed effects, and BL Hgb as a covariate. For panel B, data are adjusted LSM (SE) change from BL derived from an MMRM analysis with terms for treatment (ferric citrate vs. PBO), BL albumin, BL log iFGF23, BL TSAT, BL ferritin, week, treatment $\times$ week interaction, treatment $\times$ ferritin interaction, and treatment $\times$ week $\times$ ferritin interaction as fixed effects, and BL Hgb as a covariate. Given the skewed distribution of iFGF23, this variable was log-transformed before analysis. **$P < .01$; ***$P = .001$. CI, confidence interval; FC, ferric citrate; FER, ferritin; iFGF23, intact fibroblast growth factor 23; LSM, least-squares mean; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error; TSAT, transferrin saturation

These post hoc results indicate the association of baseline iron store markers, namely TSAT and ferritin, with hemoglobin response to ferric citrate treatment. While patients with lower baseline TSAT/ferritin experienced a greater 16-week hemoglobin increase than those with higher baseline TSAT/ferritin, hemoglobin increases versus placebo were also significant among those with higher baseline TSAT/ferritin values, indicating that ferric citrate treatment is efficacious over a wide range of patients with NDD-CKD. These data support current guidelines recommending a trial of oral iron in patients with iron deficiency anemia and CKD and

suggest the need to identify more reliable clinical markers of bone marrow iron availability.[1]

An important novel finding is the significant association of lower baseline intact FGF23 and higher baseline serum albumin with greater hemoglobin increase. No association was observed with c-terminal FGF23, presumably because cleavage of active/intact FGF23 is not impaired in the setting of iron deficiency.[5] In the setting of inflammation, serum ferritin and intact FGF23 are increased, while serum albumin is decreased.[5,6] However, serum ferritin also decreases with iron deficiency. Thus, in patients with CKD, the hemoglobin response to iron is probably dependent on various degrees of inflammation and iron deficiency anemia. This impedes the predictive utility of ferritin and even TSAT.

This study is limited by the post hoc and exploratory nature of these analyses. Results should be verified by randomized, prospective trials that focus on optimizing anemia management while achieving a steady state for iron parameters.

In summary, while hemoglobin increased in nearly all patients with iron deficiency anemia and NDD-CKD over 16 weeks of ferric citrate treatment, patients with biochemical markers of more severe iron deficiency experienced more pronounced increases in hemoglobin concentration.

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CONFLICT OF INTEREST

PEP has served as a consultant for Keryx, Akebia, Reata, Alnylam, and ExThera. SF has served as a consultant for AstraZeneca and Keryx, is on the advisory board for Keryx, has received research funding from AstraZeneca, Corvidia, Fibrogen, and Keryx, and has received honoraria from AstraZeneca and Keryx. RDL, JFN, and KU are employees of Keryx and have ownership interest in Keryx; KU is also on the board of directors for Kidney Health Initiative. GAB has served as a consultant for Akebia, Amgen, Ardelyx, AstraZeneca, Celgene, Daiichi Sankyo, Keryx, Relypsa, Sanfit, and ZS Pharma, has ownership interest in Ardelyx and Nephroceuticals, has received research support from Keryx, and has received honoraria from Akebia, Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Keryx, and Sanofi. GMC has served as a consultant to Akebia, AMAG, Amgen, Ardelyx, AstraZeneca, Gilead, and Keryx, has ownership interest in Ardelyx, Durect, Outset, PuraCath Medical, and Physiowave, has received research support from Amgen, Janssen, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Heart, Lung, and Blood Institute, and has received honoraria from the American Society of Nephrology.

AUTHORS CONTRIBUTION

PEP, SF, JFN, KU, GAB, and GMC were involved in the conceptualization and methodology of this study. PEP and GAB were involved in study investigation. PEP, JFN, and KU conducted the formal analysis. Data curation was performed by KU. RDL, JFN, and KU were involved with visualization and supervision of the study. The original manuscript draft was prepared by PEP and RDL. SF, RDL, JFN, KU, GAB, and GMC reviewed and edited the manuscript.

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SUPPORTING INFORMATION

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Dual anticoagulation with fondaparinux and dabigatran for treatment of cancer-associated hypercoagulability