

Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia

Background:

- There is a high prevalence of iron deficiency anemia in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) – it has been estimated that 48-98% of patients are affected.
- There are mixed reports of efficacy among standard over-the-counter iron formulations in NDD-CKD.

Objective:

- To determine the safety and efficacy of ferric citrate in patients with NDD-CKD suffering from iron deficiency anemia.

Methods:

- **Design:** Phase 3, double-blind, randomized controlled trial; Duration: 16 weeks with 8 week open-label extension period
- **Inclusion criteria:** men and non-lactating women 18 years of age or older; women had to have a negative serum pregnancy test at the time of screening; patients with CKD with eGFR <60 ml/min at screening (determined through MDRD equation); intolerant or previous inadequate therapeutic response to oral iron therapy; hgb \geq 9.0 g/dL and \leq 11.5 g/dL; serum ferritin \leq 200 ng/mL and transferrin saturation (TSAT) \leq 25%; serum iPTH \leq 600 pg/mL; must consume two meals per day and willing and able to give informed consent.
- **Exclusion criteria:** serum phosphate <3.5 mg/dL at screening, elevated liver enzymes 3x upper limit of normal, symptomatic GI bleeding or IBD within 12 weeks prior to screening, evidence of AKI or requirement for dialysis within 12 weeks prior to screening, scheduled kidney transplant or initiation of dialysis planned within 24 weeks of screening, IV iron administered, erythropoiesis-stimulating agent (ESA) or blood transfusion within 4 weeks prior to screening, active infection requiring antibiotics at screening, causes of anemia other iron deficiency or CKD, history of hemochromatosis, active drug or alcohol dependence or abuse, known allergic reaction to oral iron therapy, previous intolerance to oral ferric citrate.
- **Primary outcome measure:** proportion of patients achieving an increase in hemoglobin concentration of 1.0 g/dl or more from baseline
- **Secondary outcome measures:** proportion of patients who achieved a sustained treatment effect – mean change in hemoglobin from baseline >0.75 g/dL over any 4-week period of time, and mean changes in hemoglobin, transferrin saturation (TSAT), ferritin and serum phosphate
- 233 patients randomized to receive either:
 - Ferric citrate 1 g TID
 - OR
 - Placebo
- Power was expected to be >90% based on sample size of 230 patients
- Data handling method was modified intent-to-treat

Results:

- 167 patients finished the 16-week trial period and 155 patients completed the 8-week open label extension period
- **Primary outcome measure:** 52.1% of patients in the ferric citrate group achieved the 1 g/dl increase in hemoglobin compared to 19.1% in the placebo group, $P < 0.001$
- **Secondary outcome measures:** 48.7% of patients in the ferric citrate group achieved a sustained increase in hemoglobin compared to 14.8% in the placebo group, $P < 0.001$; mean relative change in TSAT between ferric citrate and placebo was 18.4% (95% CI, 14.6% to 22.2%); mean relative change in ferritin between ferric citrate and placebo was 170.3 ng/ml (95% CI, 144.9 to 195.7); mean relative change in hemoglobin between ferric citrate and placebo was 0.84 g/dl (95% CI, 0.58 to 1.10)
- **Authors' conclusion:** Ferric citrate is safe and efficacious in treating iron deficiency anemia in NDD-CKD patients

Strengths:

- All results were found to be statistically significant
- Study design was appropriate for the objective

Limitations:

- Standard deviation was reported in the baseline characteristics, but standard error of the mean was then later reported
- Differences between the two study groups at baseline
- Potential unblinding due to particular adverse effects occurring only in one group
- Short study duration that did not allow a glimpse at how the drug affects the iron stores
- Adverse effects were not statistically analyzed

Conclusion:

- Although the authors concluded that ferric citrate was safe and efficacious in treating iron deficiency anemia in patients with NDD-CKD, their evaluation had some major holes
 - The study did not focus on the clinical significance of the drug – fatigue was measured as an adverse effect, but it was not measured as a baseline characteristic so that improvement could be seen
 - The study did not measure compliance so there is no way of knowing if patients were taking the drug like they were supposed to and if they were not, the adverse effects seen could be worse
- Future research:
 - Since the objective was to determine whether ferric citrate was safe and efficacious, I think future studies need to be done that look more at clinical significance and compliance in addition to looking at endpoints such as increase in hemoglobin.

Reference: Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, et al. (2017) Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol.* 2017; 28: 1851-1858.