The Effect of Oral Ferric Citrate on Intravenous Iron Dose and Serum Iron Markers

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Introduction

- Treatment with iron and erythropoietin are necessary to promote red blood cell growth and development in patients with end-stage renal disease (ESRD) who are typically anemic. In healthy patients, approximately 30 mg of transferrin-bound iron is recycled each day from senescent red blood cells through the reticuloendothelial system.[1] Another 1 mg of dietary iron is absorbed each day through specialized enterocytes.[1] However, patients with chronic kidney disease have reduced ability to use these pathways of iron metabolism, possibly due to hepcidin hormonal disruption.[2]
- Ferric citrate is a phosphate binder currently in Phase 3 clinical development to treat hyperphoshatemia in patients with ESRD. In addition to managing patients' serum phosphorus, earlier clinical studies have shown that some iron in the drug is absorbed gastrointestinally, increasing saturated transferrin (TSAT) and serum ferritin levels.
- Study 201 was a ferric citrate open-label trial (N = 55) allowing dose titrations from 3 to 12 g/day, dependent upon serum phosphorus level.[3] In this 4-week study, some subjects received treatment with IV iron while other subjects received none. Of particular interest are 5 subjects who did not receive IV iron during the study who had received it immediately prior to study participation. Iron storage measures of these subjects may provide insight into how ferric citrate might influence patients need for IV iron therapy.

Objective

- The objective of the present analysis was to compare iron storage measures between subjects receiving IV iron prior to participating in ferric citrate Study 201 and those who did not. Our analysis emphasizes measures from the 5 subjects who had received IV iron immediately prior to starting the study but did not receive IV iron during the study.

Methods

- A 28-day, Phase 2, multicenter open-label study was conducted to assess drug safety and tolerability in study subjects receiving hemodialysis. Subjects received starting doses of 4.5 or 6.0 g/day ferric citrate, titrated until serum phosphate was in-range (3.5 to 5.5 mg/dL). IV iron therapy was allowed in patients whose ferritin was < 500 ng/mL and TSAT was < 30% at the discretion of the investigator.
- Subjects discontinued phosphate binder therapy without a washout, and began ferric citrate treatment at Visit 0 (baseline) continuing through Visit 4 for a total of 28 days. Blood for iron measures and other lab tests was drawn prior to dialysis.

Results

Table 1. Demographics, Total Population (N=55) and Subset (n=5)

N = 55	
Age (years) Mean (SD)	53.46 (11.48)
Gender Male (n)	32
Race (n)	
Black/African American	36
White/Caucasian	14
All other	5

n=5

Subject	Gender	Age	Ethnicity
951	Female	69	Not Latino or Hispanic
977	Male	57	Not Latino or Hispanic
985	Male	55	Not Latino or Hispanic
997	Female	55	Not Latino or Hispanic
1001	Male	48	Not Latino or Hispanic

Table 2. Mean Iron Measures

		Ferritin ng/mL	TIBC ng/mL	Iron ng/mL	TSAT %
IV Iron at Baseline (n=30)					
IV Iron During the Study (n=25)	Visit 0	513.9	226.6	67.5	30.1
	Visit 4	586.7	220.5	76.8	35.8
	Δ	+72.8	-6.1	+9.3	+5.7
No IV Iron During the Study (n=5)	**Visit 0**	**639.8**	**202.8**	**61.2**	**29.4**
	Visit 4	**674.4**	**212.4**	**58.4**	**27.8**
	Δ	+34.6	+9.6	-2.8	-1.6
No Iron at Baseline (n=25)					
No IV Iron During the Study (n=25)	Visit 0	603.2	233.8	71.2	30.8
	Visit 4	617.8	214.3	77.2	36.5
	Δ	+14.6	-19.5	+6.0	+5.7

Abbreviations: TIBC, total iron binding capacity; TSAT, saturated transferrin.

Table 3. Change From Baseline in Iron Measures (n=5)

Subject		Ferritin ng/mL	TIBC ng/mL	Iron ng/mL	TSAT %
951	Visit 0	341	208	74	36
	Visit 4	526	233	67	29
	Δ	+185	+25	-7	-7
977	Visit 0	950	241	112	46
	Visit 4	802	227	80	35
	Δ	-148	-14	-32	-11
985	Visit 0	946	187	46	25
	Visit 4	1005	197	41	21
	Δ	+59	+10	-5	-4
997	Visit 0	132	200	27	14
	Visit 4	120	232	40	17
	Δ	-12	+32	+13	+3
1001	Visit 0	960	195	54	28
	Visit 4	919	173	64	37
	Δ	-41	-22	+10	+9

Table 4. Mean Change From Baseline in Iron Measures for All Subjects Not Receiving IV Iron During the Study (n=30)

	Visit 0	Visit 4	P-value
Iron, ng/mL	69.8	74.1	0.35
Ferritin, ng/mL	613.6	627.2	0.63
TIBC, ng/mL	229.2	214.0	< 0.01
%TSAT	30.7	35.0	0.04

Findings/Conclusions

- In this short-term study, subjects who did not receive IV iron experienced an increase in mean serum iron, suggesting that they had some absorption of iron from treatment with oral ferric citrate. Their mean increase in serum iron combined with the slight decrease in TIBC resulted in an increase in TSAT. In these subjects, however, TSAT values remained within normal range.
- Some subjects were able to discontinue IV iron while maintaining adequate iron measures with oral ferric citrate. At the end of the study, there were no meaningful changes in iron parameters for the 5 subjects who discontinued IV iron at the begining of the study. Ferric citrate was their only source of iron for 4 weeks.
- In this short study with a small population, subjects receiving IV iron and subjects who did not receive IV iron performed similarly, suggesting that IV iron may not be be needed in all subjects receiving ferric citrate for hyperphosphatemia.
- Results from a long-term, Phase 3 clinical study of ferric citrate will be available in late 2012. Study results will provide greater insight into the need for IV iron therapy when the phosphate binder ferric citrate is administered to hemodialysis patients to treat hyperphosphatemia.

References

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