TRIFERIC DOES NOT INCREASE PREDIALYSIS HEPCIDIN LEVELS OR IRON SEQUESTRATION: THE PRIME STUDY

A. Gupta[1], D. W. Swinkels[2], V. Lin[1], C. Guss[1], R. Pratt[1]

[1]R&D, Rockwell Medical, Wixom, MI, [2]Radboud University Medical Center, Nijmegen, NETHERLANDS

ABSTRACT

INTRODUCTION AND AIMS: Uremic inflammation increases hepcidin levels leading to iron sequestration in the reticuloendothelial system (RES). Iron sequestration causes, functional iron deficiency (FID) and hyporesponsiveness to ESAs. Intravenous iron-carbohydrate complexes are nanoparticles requiring processing by the RES prior to iron release to transferrin. Furthermore, IV iron can stimulate hepcidin release and worsen iron sequestration and FID.

Soluble ferric pyrophosphate citrate (SFP, Triferic) is a small molecular weight investigational parenteral iron salt that donates iron directly to transferrin in vitro and vivo (unpublished data).

METHODS: The PRIME study randomized 108 iron-replete (baseline ferritin 200-1000 µg/L) CKD-HD patients to Triferic or placebo for up to 36 weeks. ESA could be titrated to maintain a target Hgb level (95-115 g/L), and IV iron could be administered for serum ferritin <200 µg/L. In the Triferic group at the end of treatment, prescribed ESA doses were reduced by 35% (p=0.045) and prescribed IV iron by 51% (p=0.044) vs placebo, while reticulocyte Hgb (CHr), serum soluble transferrin receptor (sTfR) and ferritin were maintained near baseline levels. In contrast, the placebo group showed a significant decrease in CHr (Δ=1.22±0.38 pg/mL; p=0.002) and ferritin, with an increase in sTfR (0.8±0.35 mg/L; p=0.03), consistent with the development of iron-restricted erythropoiesis (IRE).

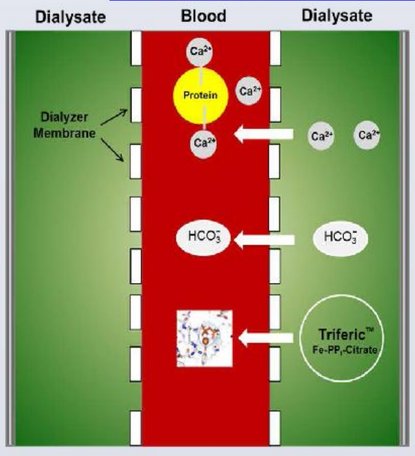
RESULTS: In patients who completed the study period, pre-dialysis serum hepcidin-25 levels were obtained at baseline and at Week 36 using mass spectrometry. Hepcidin-25 levels were similar in both groups at baseline. At week 36, when serum hepcidin levels were analyzed for individual changes from baseline values, the placebo group had a mean decrease in hepcidin-25 of 9.2 nM while the Triferic group had mean decrease of 1.9 nM.

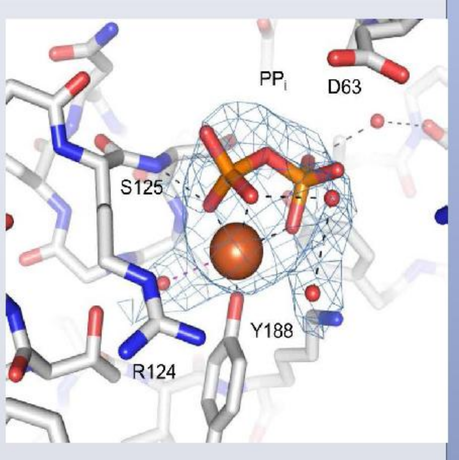
The placebo group developed evidence of IRE while the Triferic group maintained iron balance. Triferic did not increase pre-dialysis serum ferritin or transferrin saturation above baseline, and the safety profile was similar to placebo.

CONCLUSIONS: Triferic delivered via the hemodialysate represents a new paradigm for the treatment of functional iron deficiency in CKD-HD patients. Triferic replaces dialytic iron losses with no increase in serum hepcidin levels or evidence of iron sequestration.

INTRODUCTION

- Triferic is a novel, carbohydrate-free, complex iron salt delivered via hemodialysate.
- Crosses the dialyzer membrane during the hemodialysis treatment, binds immediately to apotransferrin and bypasses the RE system.
- Simply replaces the 5-7 mg iron lost with every dialysis treatment.
- Iron concentration of 2 µMol (110 µg/L) maintains iron balance without overloading iron stores.



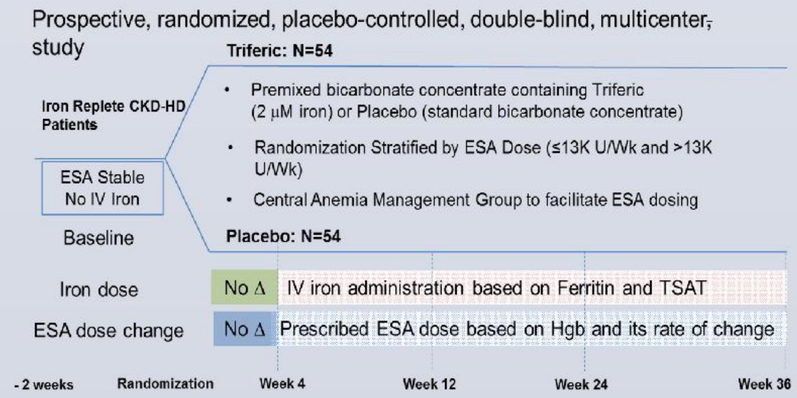


Iron crosses the dialyzer and binds to open sites on transferrin with pyrophosphate.

OBJECTIVE

- Investigate the effect of administration of Triferic Iron in the dialysate on serum hepcidin levels compared to placebo.

Study Design



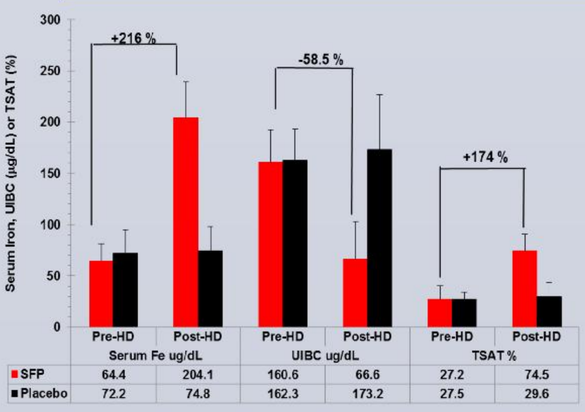
Study drug withholding:
a) pre-HD Hgb and Iron parameters:
Hgb >13.0g/dL, TSAT >50% or Ferritin >1,200 µg/L
b) bacteremia or fungemia

EoT: Last 2 weeks of treatment

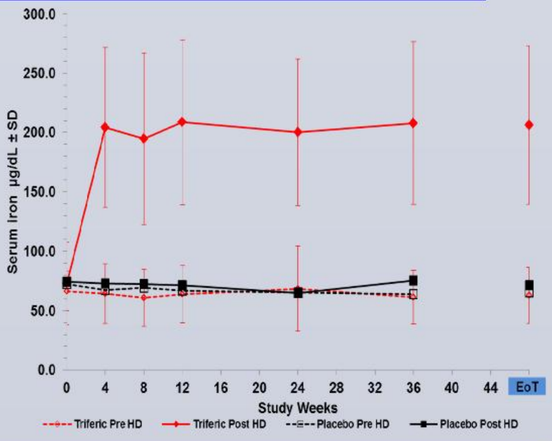
Hepcidin Measurement

- Blood was collected for Hepcidin measurement at Baseline (Pre and Post Dialysis) and at Week 36 (Pre Dialysis).
- Hepcidin-25 was measured using a Mass Spectrometry based assay (Hepcidinanalysis.com, Nijmegen, The Netherlands).

TRIFERIC RELIABLY DELIVERS IRON AT EACH HD

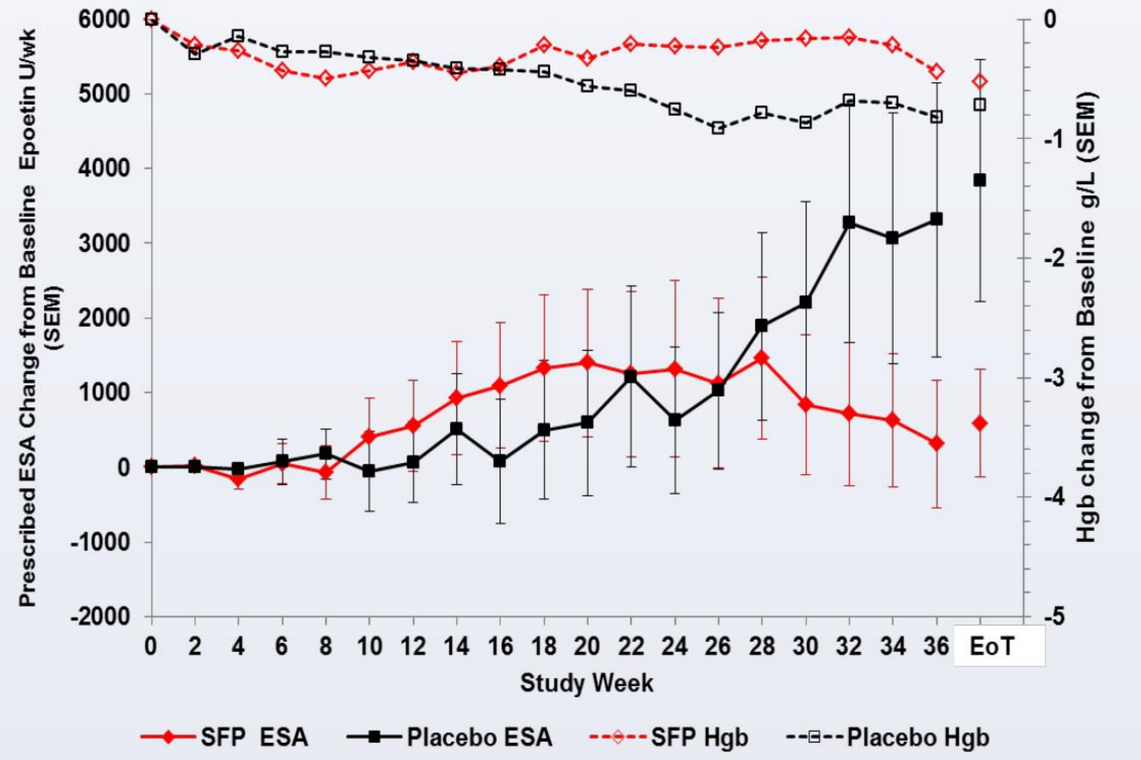


	Serum Fe ug/dL		UIBC ug/dL		TSAT %	
	Pre-HD	Post-HD	Pre-HD	Post-HD	Pre-HD	Post-HD
SFP	64.4	204.1	160.6	66.6	27.2	74.5
Placebo	72.2	74.8	162.3	173.2	27.5	29.6

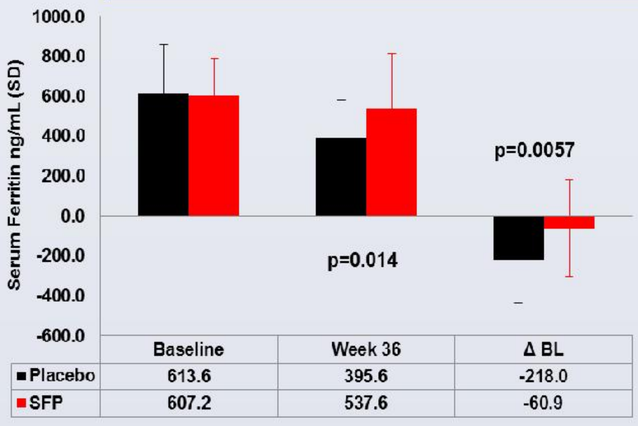


Triferic™ is a trademark of Rockwell Medical

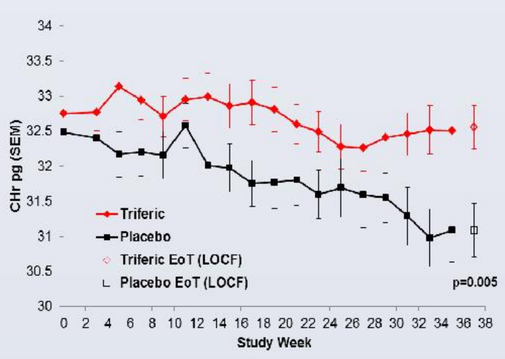
TRIFERIC MAINTAINS HGB AND SPARES ESA



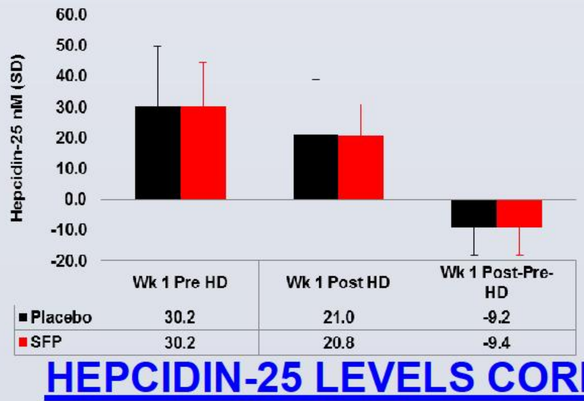
TRIFERIC MAINTAINS IRON STORES AND CHr



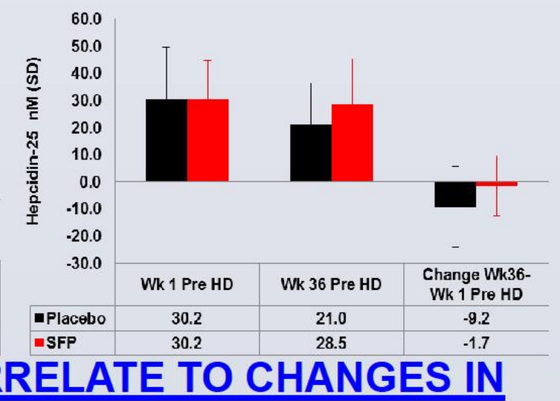
	Baseline	Week 36	Δ BL
Placebo	613.6	395.6	-218.0
SFP	607.2	537.6	-60.9



TRIFERIC DOES NOT INCREASE HEPCIDIN-25

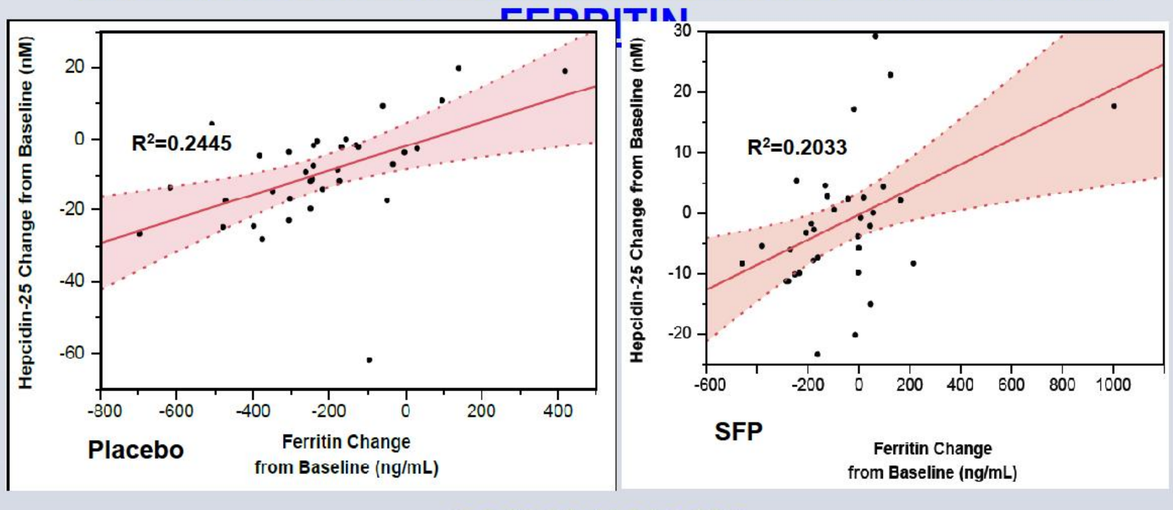


	Wk 1 Pre HD	Wk 1 Post HD	Wk 1 Post-Pre-HD
Placebo	30.2	21.0	-9.2
SFP	30.2	20.8	-9.4



	Wk 1 Pre HD	Wk 36 Pre HD	Change Wk36-Wk 1 Pre HD
Placebo	30.2	21.0	-9.2
SFP	30.2	28.5	-1.7

HEPCIDIN-25 LEVELS CORRELATE TO CHANGES IN FERRITIN



CONCLUSIONS

With each hemodialysis session (when SFP is added to the hemodialysis solutions)

- Triferic administered via dialysate reliably delivers iron during each hemodialysis
- Hepcidin-25 decreases during hemodialysis consistent with previous observations (Zaritsky et al, CJSAN 5:1010, 2010).

Triferic delivered via the dialysate during the 36 week study period:

- Maintains body iron stores (serum ferritin)
- Maintains iron delivery to the erythron (reticulocyte hemoglobin and hemoglobin).
- Does not induce oxidant stress (see poster# SP215) or inflammation (ferritin, CRP, albumin).
- Does not increase plasma Hepcidin-25 levels (consistent with maintenance of overall iron balance without any increase in inflammation).

- ***Triferic represents a new paradigm for iron replacement in CKD-HD patients.***
- ***Triferic maintains iron stores and Hgb by replacing the obligatory iron losses at each HD treatment***
- ***Triferic bypasses the RES processing step common to other IV iron products and does not increase Hepcidin-25 acutely or after 36 weeks administration***

51ERA-EDTA
482--MP
M) Dialysis. M5) Anaemia in CKD 5D.
Gupta Ajay
DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM THE NETHERLANDS MAY 31 JUNE 3 2014