Effect of Oral Ferric Maltol on Iron Parameters in Patients with Chronic Kidney Disease (CKD) and Varying Degrees of Inflammation; a Randomized, Controlled Trial

Nelson Kopyt DO, FASN, FACP
Lehigh Valley Health Network, Nelson.Kopyt@lvhn.org

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Nelson P. Kopyt – Lehigh Valley Hospital, Allentown, PA, USA
On behalf of the AEGIS-CKD Study Group

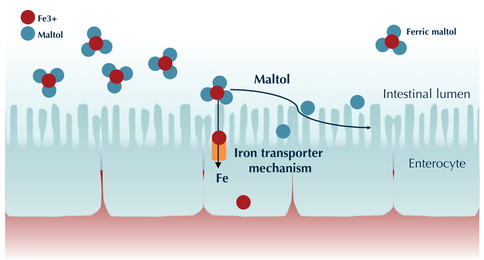
Valley Kidney Specialists, PC

Lehigh Valley Health Network

Background

- Iron-deficiency anemia (IDA) is a leading cause of morbidity and mortality in patients with CKD[1,2]
  - Intravenous iron administration can be inconvenient and risks allergic reactions or iron overload[3,4]
  - Oral ferrous treatments are associated with gastroenterological adverse events that can significantly impair compliance and efficacy[5]
  - Some patients with CKD have chronic inflammation, which can reduce the absorption and utilization of iron[6]
- Patients with CKD and IDA would therefore benefit from an oral iron-replacement therapy that is tolerable and effective irrespective of the degree of underlying inflammation
- Ferric maltol is an oral iron-replacement therapy formulated to improve gastrointestinal (GI) absorption (Figure 1)
- AEGIS-CKD was a phase III multicenter, randomized controlled trial (NCT02968368) to evaluate the efficacy of oral ferric maltol versus placebo in the treatment of IDA in adults with CKD (Figure 2)
  - Primary results for AEGIS-CKD will be presented separately (abstract #FR-OR120); here we report changes in iron storage indices for subgroups based on the degree of chronic inflammation as assessed by high-sensitivity C-reactive protein (hsCRP) levels
  - CRP is notably higher in patients with CKD than in patients with less kidney impairment:[7]
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² = mean hsCRP 4.10 mg/L (95% confidence interval [CI] 1.9–10.2)
    - eGFR >60 mL/min/1.73 m² = mean hsCRP 1.75 mg/L (95% CI 0.95–3.33) (p<0.001)

Figure 1. Mechanism of action of oral ferric maltol



Ferric maltol is a complex of ferric iron (Fe3+) and three maltol ligands. Maltol is a sugar derivative found in many food products; it strongly chelates iron in the ferric form so that it is stable and available for absorption.

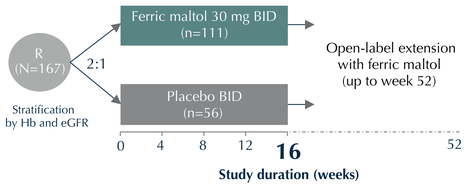
Before absorption, the ferric iron and maltol complex remains intact in the intestinal lumen, minimizing the risk of GI toxicity associated with free radicals produced by free iron. On absorption, ferric iron is bound to the iron transport receptor, and the maltol complex dissociates to be rapidly absorbed by diffusion, metabolized by glucuronidation, and eliminated by the kidneys.

Iron uptake with ferric maltol is saturable, avoiding the potential for iron overload. Unabsorbed ferric maltol is excreted intact in feces.

Figure 2. Study design

Key inclusion criteria:

- **eGFR ≥15 to <60 mL/min/1.73 m²**
- **Hb ≥8.0 to <11.0 g/dL**
  and **ferritin <250 µg/L**
  + TSAT <25%
  or **ferritin <500 µg/L**
  + TSAT <15%



Primary efficacy endpoint

Change in Hb concentration from baseline to week 16

BID, twice daily; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; R, randomization; TSAT, transferrin saturation.

Methods

- hsCRP was measured at baseline
- Changes in iron parameters (ferritin, transferrin saturation [TSAT], and serum iron) were assessed at weeks 4, 8, and 16
- hsCRP subgroups were based on the standard ranges for cardiovascular risk: low (<1 mg/L), moderate (≥1 to ≤3 mg/L), and high (>3 mg/L)
- Analyses of change from baseline to week 16 were carried out on the intent-to-treat (ITT) population (all randomized patients)
  - The least-squares mean (LSM) change from baseline was determined by analysis of covariance with treatment as a factor and continuous covariates of baseline Hb and eGFR
  - Changes in iron parameters were based on observed data, with last observation carried forward (LOCF)

Results

- 167 patients were randomized, 111 to ferric maltol and 56 to placebo (Table 1); all patients were included in the hsCRP subgroup analysis
  - 129 (77%) patients completed 16 weeks of treatment (19 [81%] in the ferric maltol group and 39 [70%] in the placebo group)
- At week 16
  - All iron parameters were significantly improved with ferric maltol vs placebo (abstract #FR-OR120)
  - The mean change from baseline in ferritin was 25.49 µg/dL (SD 5.400) with ferric maltol and –8.25 µg/dL (SD 7.614) with placebo (p=0.0004)
    - Consistent results were seen regardless of degree of underlying inflammation, as measured by baseline hsCRP level (Figure 3)
  - The mean change from baseline in TSAT was 3.78% (SD 0.638) with ferric maltol and –0.69% (SD 0.900) with placebo (p<0.0001)
    - As with ferritin, consistent results were seen regardless of degree of underlying inflammation (Figure 4)

Table 1. Patient demographics and baseline disease characteristics (ITT population)

Demographic, n (%)		Ferric maltol (n=111)	Placebo (n=56)	Total (n=167)
Age, years	Mean (SD)	68.5 (12.4)	65.2 (12.8)	67.4 (12.6)
Sex, n (%)	Female	78 (70.3)	39 (69.6)	117 (70.1)
	Male	33 (29.7)	17 (30.4)	50 (29.9)
Race, n (%)	Asian	2 (1.8)	0	2 (1.2)
	American Indian	1 (0.9)	0	1 (0.6)
	African American	23 (20.7)	12 (21.4)	35 (21.0)
	White	81 (73.0)	42 (75.0)	123 (73.7)
	Other	4 (3.6)	2 (3.6)	6 (3.6)
Hb, g/dL	Mean (SD)	10.06 (0.769)	10.03 (0.817)	10.05 (0.783)
	<9.5, n (%)	21 (18.9)	11 (19.6)	32 (19.2)
	≥9.5, n (%)	90 (81.1)	45 (80.4)	135 (80.8)
eGFR, mL/min/1.73 m²	Mean (SD)	31.9 (11.53)	29.7 (10.56)	31.1 (11.23)
	≤30, n (%)	59 (53.2)	30 (53.6)	89 (53.3)
	>30, n (%	52 (46.8)	26 (46.4)	78 (46.7)
hsCRP range, n (%)	<1 mg/L	22 (19.8)	9 (16.1)	31
	≥1 to ≤3 mg/L	26 (23.4)	17 (30.4)	43
	>3 mg/L	63 (56.8)	30 (53.6)	93

Figure 3. Mean change in ferritin from baseline to week 16 by hsCRP level at baseline (ITT population, LOCF)

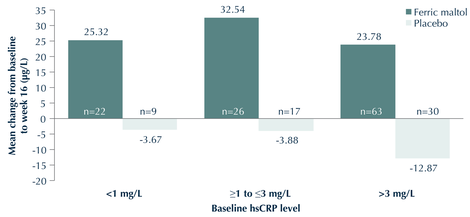
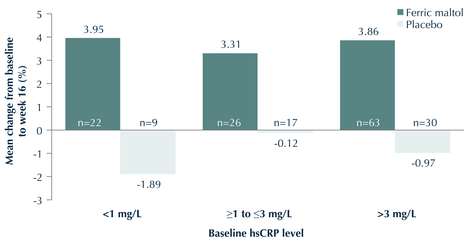


Figure 4. Mean change in TSAT from baseline to week 16 by hsCRP level at baseline (ITT population, LOCF)



Conclusion

- Ferric maltol improved iron storage parameters – ferritin and TSAT – from baseline to week 16 vs placebo in patients with IDA and CKD irrespective of the degree of underlying chronic inflammation

Acknowledgments

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SHIELD THERAPEUTICS

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Ferric maltol is not currently licensed for the treatment of IDA in CKD in the United States.

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