Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)

Lewis GD et al.

Stefan D. Anker, MD PhD

University Medicine Göttingen, Germany
s.anker@cachexia.de

Dol: Consultancy for Vifor, Luitpold, Novartis, Bayer, ASTRA, Pfizer; Grants from Vifor & Abbott Vascular; Investigator for EFFECT-HF; PI of Fair-HF & Fair-HF2
Summary

• Well done trials by expert teams

• IRONOUT: Oral iron does not work in patients with chronic heart failure.

• Iron that is not getting into the body cannot exert effects.
Results on hematinics in different trials. Change from baseline to week 16 / week 24.
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**IRONOUT-HF**

Ferritin:
- Week 0: 57 ng/ml
- Week 16: 62 ng/ml
  - Change: +11 ng/ml
  - p = 0.056

TSAT:
- Week 0: 20%
- Week 16: 21%
  - Change: +3%
  - p = 0.003

**vs. FAIR-HF (IV Iron)**

Ferritin:
- Week 0: 57 ng/ml
- Week 24: 283 ng/ml
  - Change: +238 ng/ml
  - p < 0.001

TSAT:
- Week 0: 20%
- Week 24: 22%
  - Change: +2%
  - p < 0.001

**vs. CONFIRM-HF (IV Iron)**

Ferritin:
- Week 0: 57 ng/ml
- Week 24: 71 ng/ml
  - Change: +265 ng/ml
  - p < 0.001

TSAT:
- Week 0: 20%
- Week 24: 22%
  - Change: +9%
  - p < 0.001

**vs. EFFECT-HF (IV Iron)**

Ferritin:
- Week 0: 65 ng/ml
- Week 24: 92 ng/ml
  - Change: +257 ng/ml
  - p < 0.001

TSAT:
- Week 0: 20%
- Week 24: 22%
  - Change: +2%
  - p < 0.001
Results on hematinics in different trials.
One randomised trial of oral iron vs IV iron.

Oral iron: ferrous sulfate 200 mg tid for 8 weeks (here ron polysaccharide 150 mg bd for 16 weeks)
IV iron: iron sucrose i.v. 200 mg, once a week, for 5 weeks

Oral iron: n=7
IV iron: n=10
Placebo: n=6

Beck-da-Silva L et al.
Int J Cardiol 2013.
Results on hematinics in different trials.
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Placebo: n=6

Some suggest to use iron Absorprion tests in CHF.
Levy WC. JACC 2008

The pathophysiology of iron deficiency: inflammation, hepcidin, ferroportin & the regulation of iron metabolism

Macrophages (including in liver)

Iron status ↑
Inflammation

Liver

Bone Marrow

Hepcidin

Transferrin

Erythrocytes

Macrophages

Chyme

Intestine cells (Enterocytes)

IRONOUT-HF – Hepcidin levels predict responsiveness to oral iron from baseline to week 16.

<table>
<thead>
<tr>
<th>Hepcidin at baseline, ng/mL</th>
<th>sTfR at baseline, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=114) 6.5 (3.3–11.1)</td>
<td>Placebo (n=114) 3.8 (3.3–4.8)</td>
</tr>
<tr>
<td>Oral Iron (n=111) 6.6 (3.3–10.8)</td>
<td>Oral Iron (n=111) 3.8 (2.9–4.8)</td>
</tr>
</tbody>
</table>

Higher baseline hepcidin levels were related to:

\[ \Delta \text{cellular iron levels: } \Delta \text{sTr} r=0.49, p<0.001 \]
If the patient is missing any of the required data such that a difference cannot be calculated, multiple imputation will be used to address the missing data.

Three sensitivity analyses will be performed that accounts for missing data differently.

- **Complete Case Analysis:** If the patient is missing any of the required data such that a difference cannot be calculated, the patient is excluded from that particular analysis.

- **Repeated Measures:** A repeated measures model will be used with baseline peak VO₂ as a response instead of a covariate.

- **Worst rank analysis:** Observed change in peak VO₂ will be ranked from smallest to largest. Any patient that died or had a LVAD will be assigned the worst rank.

**Statistical Tests:**

- A general linear model (PROC GLM in SAS) to compare the treatment groups.

- A mixed model (PROC MIXED) will be used to generate the repeated measures models.
Conclusions

• Oral iron does not work in patients with chronic heart failure.

• Iron that is not getting into the body cannot exert effects.

• New therapeutic modalities that can overcome the resistance to enteral iron uptake may have a chance.

• Double-blind trials make for clearer results, and hence are preferable whenever possible.

• Outcome trials in HF patients are needed. Fair-HF2 – a trial of FCM vs placebo – is about to start.