

## Intravenous iron therapy and circulating biomarkers of inflammation in men with heart failure with reduced ejection fraction

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**Background:** Large randomized clinical trials have demonstrated that intravenous (IV) iron therapy in iron-deficient patients with heart failure with reduced ejection fraction (HFrEF) brings clinical benefits related to symptoms of the disease and exercise capacity. Mechanisms underlying beneficial effects of such repletion are still the subject of interest as this is not solely related to improved haematopoiesis (IV iron works also in non-anaemic subjects). In patients with chronic heart failure iron deficiency (ID) is linked with inflammatory processes but data regarding the impact of IV iron on inflammation is scarce.

**Purposes:** We evaluated whether IV iron therapy affects circulating biomarkers of pro-inflammatory state in men with HFrEF and concomitant ID.

**Methods:** This is the sub-analysis of the study to investigate the effects of IV ferric carboxymaltose (FCM) on the functioning of skeletal muscles in men with HFrEF. For the purposes of current research we analyzed data of 20 men with HFrEF (median age 68 (62, 75 – in brackets interquartile ranges, respectively) years, LVEF: 30 (25, 35) %, ischaemic HF aetiology: 85%, NYHA class I/II/III: 30%/50%/20%) and ID (definition according to ESC guidelines - ferritin <100 ng/mL, or ferritin 100–299 ng/mL with transferrin saturation [TSAT] <20%) who were randomized in a 1:1 ratio to receive either the 24-week therapy with IV FCM (dosing scheme as in the CONFIRM-HF trial) or saline (controls). The study was double-blinded. We

used ELISA to evaluate different circulating pro-inflammatory biomarkers (high-sensitivity C-reactive protein [hs-CRP], tumor necrosis factor alpha [TNF- $\alpha$ ], interleukin 6 [IL-6], interleukin 1 beta [IL-1 $\beta$ ], interleukin 22 [IL-22]) at baseline and week 24.

**Results:** IV FCM therapy replenished iron stores in men with HFrEF as reflected by an increase in serum ferritin and TSAT, which was not seen in a control group. IV FCM therapy (as well as the saline administration) affected neither haemoglobin concentration nor parameters reflecting iron stores in red cells.

Baseline serum ferritin was not related to hs-CRP, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and IL-22 (all  $p > 0.23$ ). Baseline TSAT was related to hs-CRP ( $r = -0.47$ ,  $p = 0.02$ ) but not other inflammatory biomarkers.

Levels of hs-CRP, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and IL-22 at week 0 were similar in subjects who received IV iron and controls (all  $p > 0.22$ ).

Change from week 0 to week 24 adjusted for baseline value (delta W24-W0 as the percentage of W0) regarding IL-22 was lower in an active treatment arm as compared with saline ( $p = 0.049$ ) and there was a trend towards lower delta TNF- $\alpha$  in FCM group compared to saline ( $p = 0.067$ ). These findings were not valid for other measured pro-inflammatory biomarkers.

**Conclusions:** In men with HFrEF and concomitant ID intravenous iron therapy with FCM affects biomarkers of pro-inflammatory state. Clinical relevance of this finding requires further translational research.