Intravenous Iron Repletion in Heart Failure & the New Generation of IV Iron

IV IRON: THE STANDARD FOR IV REPLETION IN HEART FAILURE

In recent decades, a substantial amount of clinical data has come about demonstrating the importance of detecting and treating iron deficiency in heart failure (HF), and specifically, the benefits of intravenous (IV) iron repletion in this population.[1] Prior to the year 2020, IV iron had been shown to improve symptoms, exercise capacity, and quality of life (QoL) in HF patients.[2-4] The AFFIRM-AHF study published in 2020 showed that treatment with IV iron was safe and decreased the risk of hospitalizations for heart failure (HHF); it was the first trial to demonstrate that treatment with IV iron can improve major HF outcomes, and since then other trials and meta-analyses have found similar outcomes.[5,6] Multiple guidelines recommend IV iron in symptomatic HF patients with ID regardless of whether or not patients are also found to have iron deficiency anemia (IDA).[7,8] In the European Society of Cardiology (ESC) 2023 focused HF guideline update, IV iron now has a stronger, class I (previously class IIa) recommendation for use in HFrEF and HFmrEF patients in order to improve symptoms and QoL. Additionally ,the level of evidence for the use of IV iron for hospitalization reduction was modified from level B to A given the greater quality of evidence that has become available.[7]

THE LIMITATIONS OF ORAL IRON

Due to its relative ease of administration and low cost, patients and providers may desire to utilize oral supplementation to replete iron levels in ID. Unfortunately, the disadvantages of oral iron are numerous, including poor absorption and adverse effects. The challenges associated with oral iron repletion, combined with insufficient clinical data supporting its use in HF patients, have resulted in a lack of endorsement for oral products to treat ID in clinical guidelines. The adverse effects of oral iron, such as constipation, can lead to non-adherence, and it generally takes much longer time periods to replete iron orally versus intravenously given its poor absorption.[9] One retrospective study showed that after 5 months of treatment with oral iron, ferritin levels were still well below the threshold to qualify for ID.[10] In the IRONOUT trial, patients with HFrEF were given 16 weeks of treatment with 300 mg of elemental iron daily (polysaccharide iron complex), which only slightly increased TSAT by 2% and increased ferritin by 18 (8 to 38) ng/mL. No improvement was found in exercise capacity or QoL.[11]

CHALLENGES WITH OLDER IV AGENTS AND THE NEW GENERATION OF IV IRON

IV iron formulations circumvent the gastrointestinal absorption issues of oral products, thereby also bypassing many of the GI-related side effects such as constipation, diarrhea, or nausea. For stability reasons, IV iron must be formulated with a carbohydrate shell. Historically, this resulted in anaphylactic reactions from high-molecular-weight dextrans (now discontinued). With the introduction of newer iron formulations, serious adverse drug events only occur in <1 in 200,000 cases of IV iron administration. Dextran formulations, despite the lower incidence of adverse effects, still require a test dose and have longer administration times; making non-dextran formulations more attractive options. Table 1 summarizes the characteristics of various IV formulations. The most frequently used and studied formulations include iron sucrose, ferric carboxymaltose, and ferric derisomaltose.[9]

Formulation (FDA Approval)	Test Dose Needed	Typical Dose in Single Setting	FDA Indication	Evidence in HF
Iron dextran (1991)	Yes	100-1000 mg	IDA, ID from blood loss	Observational, retrospective studies
Ferric gluconate (1999)	No	125-250 mg	HD	Observational, retrospective studies
Iron sucrose (2000)	No	100-200 mg	CKD	Observational, prospective trials Small RCTs
Ferumoxytol (2009)	No	510 mg	CKD, IDA	None
Ferric carboxymaltose (2013)	No	750-1000 mg	CKD, IDA, HF	Multiple large RCTs in HFrEF
Ferric derisomaltose (2020)	No	20 mg/kg up to 2000 mg	CKD, IDA	1 large RCT Sub-analysis of RCT with some HF patients

Table 1. Intravenous Iron Formulations

In addition to their improved tolerability and lack of need to provide a test dose, the newest generation of IV iron, including ferric carboxymaltose (FCM) and ferric derisomaltose, can also provide much higher iron doses in a single dosing session. While iron sucrose is dosed at a max of 200 mg per session, FCM and ferric derisomaltose can be dosed up to 1000 or 2000 mg, respectively, as shown in Table 1. This translates to less infusion center visits for patients in order to fully replete iron deficits, and a greater chance of adherence and treatment success. Both formulations have been found to decrease HHF in recent studies, and the impact of these newer formulations of major HF outcomes continues to be an area of active study.[6]

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FOCUS ON FERRIC CARBOXYMALTOSE: FIRST IV IRON APPROVED IN HF PATIENTS

The first and only IV iron formulation that has been FDA-approved specifically for the treatment of ID in HF patients is FCM. FCM is the most extensively studied form of IV iron generally, and the greatest amount of efficacy and safety data on ID in the HF population also comes from studies of FCM.[9] The latest FDA indication awarded to FCM is for HF patients with in New York Heart Association class II/III, in order to improve exercise capacity,[12] although multiple ongoing studies continue to examine various additional outcomes across the HF spectrum.[13-16] In addition to the extensive efficacy and safety data of FCM relative to other newer formulations, another major advantage is the option for administration via slow IV push over 7.5 minutes (in addition to infusion over only 15 minutes). Infusion centers can be incredibly busy and it can be difficult to find the time to schedule all patients needing IV iron; hence this administration option may be very valuable in the practical implementation of iron repletion programs.

CONCLUSION

As more and more data become available on the benefits of ID treatment with IV iron in HF, it is becoming increasingly critical for patients and providers to have access to effective, evidence-based, well-tolerated, convenient IV iron options. FCM has emerged as a leading agent in this regard, and has recently become the only formulation of IV iron that is both guideline-recommended and FDA approved specifically for patients with HF.[7,12] IV iron repletion continues to be an area of significant research, which may result in expanded indications and improved HF outcomes.

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