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The role of iron deficiency in heart failure

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Iron is an essential micronutrient for several physiological processes in the body beyond erythropoiesis. Iron deficiency (ID) is a common comorbidity observed in about 50% of patients with stable heart failure (HF) irrespective of the left ventricular function. The presence of ID is often as a multi-factorial condition, and it is associated with exercise intolerance, reduced quality of life, increased hospitalization rate, and mortality risk regardless of anaemia. The intravenous administration of iron to correct ID has emerged as a promising treatment in HF with reduced ejection fraction as it has been shown to alleviate symptoms, improve quality of life and exercise capacity, and reduce hospitalizations.

Introduction

The importance of iron deficiency diagnosis

Despite optimal conventional therapy, many patients with heart failure (HF) continue to be symptomatic and are at high risk for repeated hospitalizations and mortality. Cardiovascular and non-cardiovascular comorbidities are frequently observed in HF; they complicate the therapeutic management and contribute to the poor prognosis of these patients.[1] Iron deficiency (ID) is a major comorbidity occurring in about 50% of patients with HF[2] and in an even higher proportion of patients with acutely decompensated HF, ranging from 72% to 83%.[3] The presence of ID in HF patients has clinical implications independently from the presence of anaemia. Iron is a critical element not only for erythropoiesis and oxygen carrying but also for energy production at mitochondrial level and in other cell processes.[4] As a consequence, ID contributes to maintain and worsen symptoms of HF such as reduced exercise tolerance and limitations in daily living activities and concurs to impair quality of life.[5] ID also increases patient mortality and morbidity, with the latter leading to a greater risk for early hospital readmission and prolonged hospitalization.[5,6] For these reasons, the 2021 European Society of Cardiology (ESC) guidelines[7] recommend to assess the iron status as part of examinations to be performed in HF patients in order to identify their needs. Making a diagnosis of ID has important practical implications: according to recent trials enrolling patients with HF with reduced ejection fraction (HFrEF), the correction of ID improved symptoms and quality of life of these patients, with preliminary data showing a positive impact on the risk of hospitalizations. These benefits have been demonstrated only for intravenous (i.v.) iron supplementation, in particular for ferric carboxymaltose (FCM), both in stable chronic patients and in those with recent acute decompensation.[8–10]

Causes and diagnosis of iron deficiency

Several mechanisms contribute to the onset of ID in HF. Gastrointestinal iron losses can be induced by the chronic administration of anti-aggregant/anti-coagulant potentially responsible for gastritis and/or duodenitis; renal dysfunction is associated with both increased urinary loss and reduced intake of proteins containing iron. The presence of oedema of the enteric mucosa can impair iron absorption determining ID. Moreover, HF is characterized by a persistent inflammatory state, in which, high levels of proinflammatory cytokines can trigger ‘iron trapping’ in macrophages, hepatocytes, and enterocytes, determining a functional ID.

In daily clinical practice, simple tests used for the diagnosis of ID include serum ferritin, serum iron, transferrin, and transferrin saturation (TSAT). International guidelines

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on HF define ID as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with transferrin saturation (TSAT) < 20%. This range has been established on the basis of the selection criteria for successful clinical use by trials of i.v. iron in HF.[9,11]

Treatment of iron deficiency in heart failure

Oral iron administration failed to improve peak oxygen uptake compared to placebo in chronic HF. Moreover, oral iron was associated with frequent gastrointestinal side effects occurring approximately in 40% of treated patients.[12] On the contrary, clinical trials showed that i.v. iron repletion therapy was effective in improving NYHA functional class, six minutes walking test distance, peak oxygen consumption, and quality of life in patients with HFrEF. The Ferinject Assessment in patients with IRon deficiency and chronic Heart failure (FAIR HF) trial was the first large-scale, double-blind, placebo-controlled trial of i.v. FCM in patients with chronic HFrEF.[9] In this study, IV FCM improved quality of life and NYHA class compared to placebo. These effects were subsequently confirmed by the FCM evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure (CONFIRM-HF) trial,[10] that documented improvements in distance walked at 6-min walk test at week 24 for the FCT arm compared to placebo, and by the Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency (EFFECT-HF) study that showed significant improvements of VO_2 peak after FCM.[11] Even if no clinical trials have been designed to demonstrate the benefit of iron therapy on hospitalizations and deaths in patients with HF, some promising preliminary data have been reported: the CONFIRM-HF trial,[10] as a secondary endpoint, showed a significant reduction in the risk of hospitalizations for worsening HF in the FCM arm compared to placebo, whereas the number of deaths was similar between groups. This positive impact of iron repletion therapy on hospitalization, cardiovascular, and total mortality has been confirmed in two recent meta-analyses.[13,14] Further adequately powered RCTs are needed to confirm the beneficial effects of iron repletion therapy on strong clinical endpoints.

The AFFIRM-AHF[15] trial for the first time assessed the effects of i.v. FCM in the acute setting: the study enlisted patients with HFrEF who were hospitalized for acute HF and presented ID. The administration of i.v. FCM was started before discharge and continued during the follow-up. The trial showed that treatment with FCM improved symptoms, quality of life, and exercise tolerance in this population; moreover, it reduced the risk of re-hospitalizations for HF compared with placebo.

Potential impact of iron repletion therapy on healthcare costs

Results of clinical trials on i.v. iron therapy, in particular the AFFIRM-AHF study, indicate that the correction of ID could positively impact the prognosis of those patients with HFrEF who are at advanced stages of the disease and are characterized by a high rate of hospitalizations. From an economic point of view, by reducing hospital admissions, iron repletion therapy could have a role in relieving the heavy financial burden on healthcare systems that is mainly due to the high rate of early readmission for worsening HF. The economic value of i.v. FCM for the treatment of ID in patients stabilized after an acute decompensation episode has been recently assessed in a cost analysis involving the US and some European countries. The study indicated that the treatment is cost-effective in all evaluated countries and cost-saving in some of them.[16] A study on cost-effectiveness in the Italian healthcare system showed that treatment with FCM in HF patients could lead to national budget annual savings of 20–97 million euros, according to different utilization rates.[17] However, although current guidelines for the treatment of chronic and acute HF acknowledge the importance of ID correction and recommend intravenous iron supplementation for its treatment, ID remains frequently underdiagnosed and undertreated. According to data coming from the CARMES-1 registry, in Italy, among HF patients diagnosed as ID during the hospitalization, only 11% of them reached the haemoglobin target value after a 4-week from discharge.[18]

Guideline recommendations

Data from real life showing that the assessment of iron status is often neglected in HF despite ID being a very common finding have made ID defined as an ‘unmet need’ of HF patients. In order to improve the general awareness of physicians, the latest European guidelines underlined the opportunity to assess iron status in all patients hospitalized for HF exacerbations, and to start treating those with ID. At the same time guidelines recommended periodic re-assessment of iron status and anaemia in all patients during the post-discharge phase with a full evaluation of blood cells count, serum ferritin concentration, and transferrin saturation.[7] Iron repletion therapy has also been enforced, in patients with chronic HF who are symptomatic, despite receiving optimal background HF therapy.[7] The only exception is represented by patients with haemoglobin levels >15 g/dL, since the efficacy of i.v. iron repletion therapy has not been tested in these patients. Determination of the initial iron need can be calculated based on body weight and haemoglobin levels. In the case of FCM, the maximum recommended cumulative dose is 1000 mg iron (20 mL FCM)/week. After the correction of ID, as part of routine follow-up, it is recommended the re-evaluation of iron parameters (ferritin and TSAT) 1–2 times per year. However, iron status should be re-evaluated if patients remain symptomatic despite receiving optimal background HF medications, or in the event that haemoglobin levels decrease. It is recommended to re-evaluate iron status 3 months after the administration of a correct dose of iron, and further iron repletion should be administered if needed. If there is no response or haemoglobin levels decrease, further investigation for other underlying causes should be considered as clinically indicated, particularly occult blood loss.

Conclusion

ID has a negative impact on HF patients in both acute and chronic settings. The use of i.v. FCM for correcting ID in patients with HFrEF, in addition to the standard medical management, has been shown to improve exercise tolerance, and quality of life, and to reduce hospitalization in both stable patients and in those with recent acute HF

exacerbations. New adequately powered RCTs are needed to verify its effects on hospitalizations and deaths. Moreover, further studies will have to evaluate the effects of i.v. iron administration in patients with preserved EF.

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Data availability

No new data were generated or analyzed in support of this paper.

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