nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Brief review

Heart failure in patients with kidney disease and iron deficiency: The role of iron therapy☆

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ARTICLE INFO

Article history:
Received 14 November 2016
Accepted 27 March 2017
Available online 23 November 2017

Keywords:
Iron deficiency
Heart failure
Chronic kidney disease
IV iron therapy

ABSTRACT

Chronic kidney disease and anaemia are common in heart failure (HF) and are associated with a worse prognosis in these patients. Iron deficiency is also common in patients with HF and increases the risk of morbidity and mortality, regardless of the presence or absence of anaemia. While the treatment of anaemia with erythropoiesis-stimulating agents in patients with HF have failed to show a benefit in terms of morbidity and mortality, treatment with IV iron in patients with HF and reduced ejection fraction and iron deficiency is associated with clinical improvement. In a *post hoc* analysis of a clinical trial, iron therapy improved kidney function in patients with HF and iron deficiency. In fact, the European Society of Cardiology's recent clinical guidelines on HF suggest that in symptomatic patients with reduced ejection fraction and iron deficiency, treatment with IV ferric carboxymaltose should be considered to improve symptoms, the ability to exercise and quality of life. Iron plays a key role in oxygen storage (myoglobin) and in energy metabolism, and there are pathophysiological bases that explain the beneficial effect of IV iron therapy in patients with HF. All these aspects are reviewed in this article.

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DOI of original article:
http://dx.doi.org/10.1016/j.nefro.2017.03.027.

☆ Please cite this article as: Cases Amenós A, Ojeda López R, Portolés Pérez JM, en representación del Grupo de Anemia de la S.E.N. Insuficiencia cardíaca en la enfermedad renal y déficit de hierro: importancia de la ferroterapia. Nefrologia. 2017;37:587–591.

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◊ A list of the members of the group can be found in Appendix A.

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Insuficiencia cardíaca en la enfermedad renal y déficit de hierro: importancia de la ferroterapia

Palabras clave:
Déficit de hierro
Insuficiencia cardíaca
Enfermedad renal crónica
Ferroterapia intravenoso

RESUMEN

La enfermedad renal crónica y la anemia son frecuentes en la insuficiencia cardíaca (IC) y su presencia se asocia con un peor pronóstico en estos pacientes. La ferropenia es frecuente en pacientes con IC y aumenta el riesgo de morbimortalidad, independientemente de la presencia o no de anemia. Mientras el tratamiento de la anemia con agentes estimuladores de la eritropoyesis en pacientes con IC no ha demostrado un beneficio sobre la morbimortalidad, el tratamiento con hierro intravenoso (iv) en pacientes con IC y fracción de eyección disminuida y déficit de hierro se asocia con una mejoría clínica. Además, en un análisis *post hoc* de un ensayo clínico, la ferroterapia mejoró la función renal en pacientes con IC y ferropenia. De hecho, las recientes guías clínicas sobre IC de la Sociedad Europea de Cardiología señalan que se debe considerar el tratamiento con hierro carboximaltosa iv en pacientes sintomáticos con fracción de eyección disminuida y déficit de hierro a fin de mejorar los síntomas, la capacidad de ejercicio y la calidad de vida. El hierro juega un papel importante en el almacenamiento de oxígeno (mioglobina) y en el metabolismo energético, y existen bases fisiopatológicas que explican el efecto beneficioso de la ferroterapia iv en pacientes con IC. Todo ello es revisado en el presente artículo.

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Introduction

Anaemia is a common complication in heart failure (HF) patients and is associated with more symptoms, worse functional class, a higher rate of hospitalisation and greater mortality.[1,2] In addition, changes in anaemia status during follow-up in patients with HF modify the risk of mortality.[3] The presence of chronic kidney disease (CKD) is also very common in this population, and the prevalence of HF increases as the glomerular filtration rate decreases.[4] In addition, anaemia is more prevalent in patients with HF and CKD.[5] This complication is therefore emerging as a potentially modifiable and important factor in the treatment of chronic HF.[1,6] The presence of CKD or anaemia are associated with increased morbidity and mortality in HF, and the interaction of a decreased glomerular filtration rate and low haemoglobin level on mortality are additional risk factors.[7] The causes of anaemia in HF include: iron deficiency, renal dysfunction and neurohormonal activation and the presence of pro-inflammatory cytokines resulting in a deficient production of erythropoietin and impaired utilisation of iron, as well as malnutrition, which is common in these patients; haemodilution also contributes to anaemia.

Treatment of anaemia in patients with HF with erythropoiesis-stimulating agents (ESAs) presented promising results in pilot studies that have not been confirmed in controlled clinical trials. The large clinical trial specifically designed to analyse events and mortality, the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial,[8] has not demonstrated benefits in the primary composite outcome of mortality and hospital admission for HF in these patients. In addition, a recent meta-analysis of the treatment of anaemia with an ESA in patients with HF concluded that it improves the symptoms (dyspnoea and quality of life), but it has a neutral effect in terms of mortality or readmission rate, and an increased risk of thromboembolic events.[9]

Therefore, recently the focus has been on iron therapy, as it is well known that iron deficiency has a negative effect that goes beyond the generation of anaemia in HF.

Iron deficiency in heart failure

Clinical guidelines and consensus documents define iron deficiency in patients with HF based on ferritin levels <100 μg/l or between 100–300 μg/l with transferrin saturation <20%. It is estimated that between 30% and 50% of patients with HF have iron deficiency.[10,11] Iron deficiency may cause anaemia, but it also has a direct harmful effect on myocytes.[10,11] Both pathophysiological mechanisms explain the relationship between iron deficiency and the risk of morbidity and mortality in HF, which is independent of the haemoglobin level.[11–13] These data have positioned iron deficiency as a new therapeutic target for these patients.[10–13]

In fact, in two randomised trials in patients with HF and iron deficiency, intravenous (IV) iron therapy had a beneficial effect.[14–16] The study "Ferinject assessment in patients with iron deficiency and chronic heart failure" (FAIR-HF) showed that treatment with ferric carboxymaltose for six months improved quality of life, functional class according to the NYHA classification and exercise capacity, both in anaemic and non-anaemic patients.[14,15] In the "Ferric CarboxymaltOse evaluatioN on per-Formance in patients with IRon deficiency in coMbination with chronic Heart Failure" (CONFIRM-HF) study, improved exercise capacity, symptoms and quality of life; reduced the risk of hospitalisation due to exacerbation of HF in patients with HF and reduced ejection fraction (HR: 0.39; 95% CI: 0.19–0.82; $p = 0.009$).[16] In addition, in a sub-analysis of the FAIR-HF study, an improvement in renal function was

observed with this treatment.[17] More recently, in another small study on HF patients with, CKD and iron deficiency anaemia, IV iron therapy was associated with an improvement in myocardial function and heart dimensions.[18] Finally, a recent meta-analysis on the effect of IV iron therapy in patients with HF with reduced ejection fraction and iron deficiency demonstrated a reduction in the composite endpoint of all-cause mortality, cardiovascular death or hospitalisation for HF (OR 0.39; 95% CI: 0.24–0.63; $p = 0.0001$), improvement in functional class (−0.54 class, 95% CI: −0.87 to −0.21; $p = 0.001$), improvement in symptoms (patient global assessment +0.70 points; 95% CI: 0.31–1.09; $p = 0.0004$), exercise capacity (+31 m, 95% CI: 18–43; $p < 0.0001$), in the six-minute walk test and quality of life measured by different scales.[19]

Given the lack of evidence of benefits from oral iron therapy and the benefit observed with IV ferric carboxymaltose in patients with congestive HF and iron deficiency, it is recommended the administration of IV iron in these patients.[20] In fact, recent guidelines from the European Society of Cardiology (ESC) on HF indicate that treatment with IV ferric carboxymaltose should be considered in symptomatic patients with HF and reduced ejection fraction with iron deficiency in order to improve symptoms, exercise capacity and quality of life (class IIa recommendation and level of evidence A).[21] However, the same guideline highlights that no clinical trial had sufficient statistical power to evaluate the effects on hard clinical events (mortality or cardiovascular events) or to analyse separately the effects on anaemic vs. non-anaemic patients. Finally, the effect of treating iron deficiency in patients with HF and preserved or slightly reduced ejection fraction, and long-term safety of IV iron in this population are unknown. There are currently a number of ongoing clinical trials analysing the effect of administering IV iron on clinically relevant events "Study to compare ferric carboxymaltose with placebo in patients with acute heart failure and iron deficiency" [Affirm-AHF] NCT02937454, "Effectiveness of intravenous iron treatment vs. standard care in patients with heart failure and iron deficiency: A randomised, open-label multicentre trial" [IRONMAN] NCT02642562, or the "Intravenous iron in patients with severe chronic heart failure and chronic kidney disease" NCT00384567 that will answer definitively if the benefit of iron therapy in patients with HF and iron deficiency also applies to hard events and improves prognosis in these patients.

Pathophysiology of iron deficiency in heart failure

Is there a pathophysiological basis explaining this improvement in HF after administration of IV iron, regardless of the presence of anaemia? Iron is essential in the physiology of the myocardiocyte, such as oxygen transport and storage, and energy metabolism (it is a component of the mitochondrial electron transport chain).[22,23] The heart has the highest metabolic demands of the body, and the production of energy, determined to a large extent by mitochondrial function, should adapt to energy requirements.[24] At the tissue level, the iron content in the myocardium is reduced by 20–30% in patients with severe HF.[25,26] Thus, small changes in the cardiac energy metabolism may have a significant effect on myocardial contractility. The availability of iron is regulated by two iron regulatory proteins: iron regulatory elements IRP1 and IRP2. In the presence of Iron deficiency, the IRPs interact with iron-responsive elements increasing the stability of the transferrin receptor mRNA and inhibiting the translation of ferroportin and ferritin H- and L-chains which promotes the increase in intracellular iron.[27] A recent study has shown that the activity of IRPs is reduced in HF, which is associated with reductions in transferrin receptor gene expression and tissue concentration of iron.[28] These findings have been confirmed in another study which also demonstrated an association with myocardial mitochondrial dysfunction in patients with HF.[29] In the aforementioned publication, the effect of the selective deletion of IRP1 and IRP2 was analysed in the myocardium in an experimental model.[28] These mice were unable to increase the left ventricular function in response to a dobutamine stress test. After a myocardial infarction, they developed a more severe left ventricular dysfunction and had a higher mortality rate due to HF. In addition, the activity of the mitochondrial electron transport chain was decreased in these mice. In another animal model, the specific deletion of the transferrin receptor in the myocardium was associated with myocardial iron deficiency and severe cardiomyopathy.[30] In both models, these changes were reversed with the systemic administration of iron.[28,30]

A recent pilot study on patients with HF and iron deficiency reported that the administration of IV ferric carboxymaltose was associated with myocardial iron repletion measured by cardiac magnetic resonance imaging, which was associated with left ventricular remodelling.[31] Thus, there is evidence of decreased myocardial iron content in HF, and that cellular iron plays a role in the energy generation processes through the mitochondrial respiratory chain. Therefore, a decrease in myocardial iron content could contribute to the pathophysiology of HF. Systemic administration of iron may reverse this situation and improve clinical symptoms in patients with HF.

In summary, HF is highly prevalent in patients with CKD, and vice versa. Iron deficiency is common in this population, and it is associated with a worse prognosis, regardless of the presence of anaemia. The studies completed to date show a beneficial effect of treatment with IV iron therapy in patients with HF with reduced ejection fraction and iron deficiency, regardless of the presence or absence of anaemia. Therefore, in these patients, assessment of iron status and considering the treatment of the iron deficiency is recommended. This represents a conceptual change in patients with HF and CKD compared to what is stated in the treatment guidelines for anaemia in CKD, where iron therapy is only indicated in the presence of anaemia and iron deficiency.

Nephrologists are responsible for the treatment of anaemia in patients with CKD, and act are experts in the management of parenteral iron therapy in CKD and, by extension, in related fields. We should be prepared to join cardiologists in these cases, which are on the borderline between the two specialities. The knowledge and experience accumulated in the management of anaemic patients with CKD may be useful in paving the way for our cardiologist or internal medicine colleagues in the new indications for iron therapy.

Key concepts

- Iron deficiency with and without anaemia is common in patients with HF, and increases the risk of morbidity and mortality, regardless of the presence or absence of anaemia.
- Iron deficiency in HF is defined by ferritin levels <100 μg/l or 100–300 μg/l if it is associated with a transferrin saturation level <20%.
- There are pathophysiological bases that explain why the correction of iron deficiency in patients with HF and reduced ejection fraction improves the actual clinical situation and the overall prognosis.
- The use of parenteral iron therapy, but not ESA, in iron deficient HF patients with reduced ejection fraction improves symptoms, exercise tolerance, quality of life and reduces readmissions. The effects of IV iron therapy on mortality and morbidity are being evaluated in ongoing randomised clinical trials.
- In patients with symptomatic HF with reduced ejection fraction and iron deficiency, the administration of IV iron as ferric carboxymaltose should be considered regardless of the presence of anaemia, as presented in the recent HF guidelines from the ESC[21] and the consensus document from the Spanish Society of Cardiology (SEC) and the Spanish Society of Internal Medicine (SEMI).[32] This assumption would be extended to patients with HF and iron deficiency who also have CKD.
- After the correction of iron deficiency in these patients, the maintenance doses will depend on the blood count values and the iron kinetics prior to the new dose, in order to avoid an iron overload.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A.

Anaemia Group of the Spanish Society of Nephrology (SEN): José María Portolés, coordinator; Ángel Luis Martín de Francisco, Manuel Arias, Pedro Aljama, Juan Manuel López Gómez, José Luis Górriz, Alberto Martínez-Castelao, Aleix Cases, Patricia de Sequera, Borja Quiroga, Raquel Ojeda and Sagrario Soriano.

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