

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. *Nefrología*. 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 feroterapia

R E S U M E N

Palabras clave:

Déficit de hierro
Insuficiencia cardíaca
Enfermedad renal crónica
Ferroterapia intravenoso

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 feroterapia 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 feroterapia 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 performance 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

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