Anemia and iron in internal medicine: an Italian survey and a review on iron intravenous therapy in medical patients

Andrea Montagnani,[1] Stefania Frasson,[2] Gualberto Gussoni,[2] Francesco Dentali,[3] Andrea Fontanella,[4] Dario Manfellotto[5]

[1]Internal Medicine, Hospital of Misericordia, Grosseto, Italy; [2]Department of Clinical Research 'Centro Studi', FADOI Foundation, Milan, Italy; [3]Internal Medicine, ASST 'Sette Laghi', Varese, Italy; [4]Internal Medicine, Hospital 'Buon Consiglio - Fatebenefratelli', Naples, Italy; [5]Internal Medicine, Hospital 'San Giovanni Calibita - Fatebenefratelli Isola Tiberina', Roma, Italy

ABSTRACT

In Italy, Internal Medicine Units hospitalize approximately 1,300,000 patients, often elderly and comorbid. The prevalent diagnoses are respiratory diseases, heart failure, or pneumonia. As a matter of fact, anemia is probably underestimated in the compilation of the official discharge forms (SDO) according to ICD-9 diagnostic codes. We promoted a survey among the Members the Italian Scientific Society of Internal Medicine (FADOI) with the aim to investigate the prevalence of anemia and iron deficiency, over than certain aspects related to the therapeutic management of patients with anemia. Furthermore, we performed a review summarizing current evidence for iron intravenous therapy in these patients. According to the survey, anemia is present in around half of the patients hospitalized in Internal Medicine, and about a quarter of them shows iron metabolism alterations. In the evaluation of iron metabolism, the dosage of ferritin is the most requested exam, whereas transferrin saturation is less considered. By focusing on some categories of patients, the awareness of the usefulness of intravenous iron therapy in patients with heart failure seems to be sufficiently common (76% of physicians), while it seems lower (60%) in the management of patients with chronic kidney disease (CKD) and anemia. Finally, more than 75% of the physicians answered that, in their hospital, there are few outpatients' offices or diagnostic pathways dedicated to patients with anemia. Anemia due to absolute or functional iron deficiency is particularly prevalent in Internal Medicine inpatients. For this reason, an accurate evaluation of iron profile and an adequate iron therapy is mandatory in these patients. Recent studies show that, in patients with heart failure, intravenous iron therapy is an effective way of improving patients' health, regardless of the presence of anemia. Similarly, iron therapy results fundamental to optimize erythropoiesis-stimulating agent efficacy in patients with chronic renal failure. In the next future, other therapeutic aspects of intravenous iron therapy will be probably clarified by several interesting ongoing studies focused on these patients.

Correspondence: Andrea Montagnani, Internal Medicine, Hospital of Misericordia, via Senese, 58100 Grosseto, Italy.
E-mail: montagnaniand@gmail.com

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Introduction

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exam, whereas transferrin saturation is less considered. By focusing on some categories of patients, the awareness of the usefulness of intravenous iron therapy in patients with heart failure seems to be sufficiently common (76% of physicians), while it seems lower (60%) in the management of patients with chronic kidney disease (CKD) and anemia. Finally, more than 75% of the physicians answered that, in their hospital, there are few outpatients' offices or diagnostic pathways dedicated to patients with anemia.

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Introduction

About 9,000,000 of patients are hospitalized every year in Italy. Among them, about 50% refers to medical wards. In Italy, Internal Medicine Units hospitalize approximately 1,300,000 patients per year.[1] According to data retrieved from the official discharge forms, the most frequent diagnoses in Internal Medicine are pulmonary oedema with respiratory failure (diagnosis related group DRG 087; 12.1%), heart failure with shock (DRG 127; 8.4%), pneumonia (DRG 089; 5.1%), septicemia without mechanical ventilation (DRG 576; 4.7%), intracranial hemorrhage or cerebral infarction (DRG 014; 4.7%) and renal failure (DRG 316; 3.3%). The DRG 395 (red blood cell abnormalities) accounts for 1.2% of the diagnoses, a figure probably underestimated due to the habit of Internists of not including anemia among the prevalent diagnoses in compiling the official discharge forms. Therefore, uncertainty exists about the real prevalence of anemia or of iron deficiency among hospitalized patients, underestimated issue according most recent systematic reviews.[2]

Survey

With the aim of answering to these needs of knowledge, the Italian Scientific Society of Internal Medicine (FADOI) promoted a survey among its Members (around 2500), containing 14 questions referred to the prevalence and the therapeutic management of anemia and iron deficiency (Table 1).

Answers to the questionnaire were collected from about 30% of the Members of the Society, with a well-representative geographical distribution.

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Table 1. Questions included in the survey.

1	What percentage of your hospitalized patients have anemia?
2	In your experience on the ward, what percentage of hospitalized patients with anemia have an iron deficiency?
3	When evaluating anemia in an outpatient or hospitalized patient, when do you request a reticulocyte count? In an outpatient or hospitalized anemic patient?
4	Which of the following tests do you request when in evaluating iron metabolism? (multiple answer)
5	When treating sideropenic anemia in an outpatient setting, do you mainly prescribe oral or intravenous iron therapy?
6	When treating sideropenic anemia in a hospitalized patient, do you mainly prescribe oral or intravenous iron therapy?
7	In your experience of oral iron therapy, what is the success rate (iron profile correction and Hb >10 g/dL) in a recommended guideline time of 3 months?
8	In your experience of intravenous iron therapy, what is the success rate (iron profile correction and Hb >10 g/dL) in a guideline time of 3 months?
9	In your opinion, what Hb threshold would be appropriate to perform a blood transfusion with packed red blood cells, in a hemodynamically stable patient?
10	Does your department have an outpatient clinic dedicated to evaluating anemic patients?
11	Is there a diagnostic treatment pathway in your hospital for patients with sideropenic anemia?
12	Do you think that intravenous iron therapy in heart failure patients helps to achieve health objectives more quickly and effectively?
13	Do you think that intravenous iron therapy in CRF patients helps to achieve health objectives more quickly and effectively?
14	How many patients per month are treated with intravenous iron therapy in your Unit?

Hb, hemoglobin; CRF, chronic renal failure.

present in around half of the patients hospitalized in Internal Medicine (47.2%, range: 30-60%), and that among these, about 45% present specific characteristics of iron deficiency (range: 18-54%).

By considering the evaluation of the patient with anemia, reticulocytes are 'always', 'often' and 'never' counted in 39%, 46% and 15% of cases, respectively.

Ferritin is the most requested exam in the evaluation of iron metabolism (98.5%). Transferrin is evaluated in 78% of cases and transferrin saturation (TSAT) in 38.7%. These data seem to confirm a need for improvement in considering the value of TSAT, which is important in identifying some conditions of functional iron deficiency that can be related to forms of anemia related to chronic diseases, and very frequently found in fragile and complex patients such as those referring to Internal Medicine wards.

In the treatment of iron deficiency, Internists mainly prescribe oral therapy to outpatients (89.5%) and intravenous therapy to hospitalized patients (82%). The perception of the effectiveness of iron therapy is estimated to be only around 50% for the oral form, rising to 90% for the intravenous one.

These responses were rather expected. Indeed, the endovenous iron treatment is more easily performed during hospitalization thanks to the presence of venous accesses and the constant monitoring of the nursing staff. Furthermore, the need of targeting a rapid therapeutic response should be considered in acute hospital settings.

The survey showed that the awareness of the usefulness of the intravenous iron therapy seems to be sufficiently common in patients with heart failure (76% of Physicians), being a little lower (60%) for the management of patients with chronic renal insufficiency and anemia.

Finally, the survey wanted to investigate even some organizational aspects. With a similar geographical distribution, more than 75% of the Physicians answered that, in their hospital, there is no outpatients' offices dedicated to patients with anemia. Furthermore, only the 32% of the participants confirmed the presence of a diagnostic-therapeutic pathway (PDTA) dedicated to the diagnosis and treatment of anemia.

Iron therapy in an Internal Medicine patient

An Internal Medicine patient usually has multiple comorbidities, which complicates the diagnostic work up of iron deficiency and associated anemia.[3]

In fact, an absolute iron deficiency may occur in the face of an increased need for iron, as well as a reduced intake, a decreased intestinal absorption or an increased loss. Decreased absorption is found in patients with gastritis due to gastric pH changes, or in patients with *Helicobacter pylori* infection or inflammatory bowel disease. The use of proton pump inhibitors (PPIs) may result in decreased iron absorption. All these conditions are, obviously, very little corrected by oral iron supplements.

Chronic loss of blood, and consequently iron, may be present in elderly patients with wall lesions due to non-steroid anti-inflammatory drugs use or abuse, in patients requiring anticoagulant therapy, or in patients with intestinal cancer that bleeds easily.

Conversely, a functional iron deficiency can mainly occur in patients with a reduced availability of iron towards the bloodstream, such as in chronic inflammatory conditions [chronic renal failure (CRF), heart failure (HF), chronic infections, autoimmune diseases or cancer] or when erythropoiesis is particularly active in response to acute anemia or erythropoietin therapy.

The prevalence of anemia in patients hospitalized in Internal Medicine departments is quite high, ranging between 48% and 67% depending on the authors,[3,4] similarly to our findings from the survey.

However, due to the characteristics of medical patients (*e.g.*, old age and multiple co-morbidities) anemia is often due to a variety of factors and the normal values defining the iron profile (in particular ferritin) are inadequate for a correct diagnosis. In particular, the term 'unexplained' anemia is often wrongly used, especially when it refers to conditions that has not been sufficiently or appropriately studied.[5]

A recent expert consensus recommended a ferritin threshold below 100 ng/mL to diagnose IDA in elderly or post-operative patients and in patients with chronic inflammation,[6] whereas transferrin saturation (TSAT) should be below 20% in chronic inflammatory conditions, or even <16% in hospitalized medical patients.

Oral iron remains the first line of treatment in all patients with asymptomatic IDA due to its affordability and ease of administration. There are countless formulations of iron salts or complex polysaccharides. 'Pharmacological' iron taken in this way follows the same path of the supplement: it passes from the lumen to the enterocyte through the DMT1 (divalent metal transporter 1) and this mechanism makes iron salts popular. However, it is important to take in mind that the salt titre given (*e.g.*, 105 mg Fe in 305 mg FeS), is not identical to dosage of elemental iron (100-200 mg/day) should be administered. Therefore, we should always refer to iron element rather than salt dosage.

Unfortunately, the oral preparations are frequently associated with gastrointestinal adverse events, such as nausea, vomiting, epigastralgia, heartburn, constipation or diarrhea, mainly due to toxicity on intestinal mucosa of the not absorbed iron. Two recent meta-analyses, involving several thousand patients, reported the occurrence of these adverse events as between 30% and 70%.[7,8]

Poor adherence to therapy and prolonged treatment times (several months) can result in under-treatment of the IDA in the daily clinical practice. What is more important, patients affected by gastro-intestinal disorders, which in themselves reduce iron absorption, respond even worse and with even more extended time frames, further compromising patient compliance. In all these cases, the use of IV iron is potentially the most effective route of administration.

Intravenous iron therapy became clinical practice in the second half of last century. The first preparations had the same composition as those used today: an iron center covered in a carbohydrate shell. The reason for this choice was to minimize the concentration of Fe(III) ion in the bloodstream due to its known toxic effects. Unfortunately, the first shell used was made from high molecular weight dextran. Although effective in correcting IDA, some cases of severe, sometimes fatal, anaphylactic reactions occurred. This helped to create the image of a 'dangerous' preparation, a prejudice still presents among physicians despite the recent evolution in the technology of these preparations. In particular, the carbohydrate shells have been improved to make the structures more stable (less Fe ion release) and the shells less immunogenic. Carbohydrate shell not only stabilizes nanoparticles of iron-carbohydrate complex but also it seems to influence pharmacodynamic and pharmacokinetic aspects. However, nanoparticles characteristics namely depend on production process as well as biological drugs, suggesting that efficacy and safety data obtained for a single product cannot automatically transfer to other similar products.[9]

To date, three new preparations, ferric carboxymaltose (FCM), iron isomaltoside and ferumoxytol, became available on the market with important effects on Internal Medicine patients with absolute or relative IDA.[10]

Iron therapy and heart failure

The link between anemia and heart failure (HF) was highlighted at the beginning of the century thanks to studies showing how anemia worsened the prognosis in these patients.[11] Subsequent attempts to improve survival by correcting anemia using ESA (especially darbepoetin) failed, leading to the suspicion that hemoglobin itself was not the factor impacting the disease.[12]

At the same time, a line of research focusing on the possible role of iron, showed that iron deficiency, regardless of the presence of anemia, reduced the survival in these patients.[13]

The main hypothesis was based on the ubiquitous presence of iron in the human body, including the heart muscle. In addition to the role of iron as a component of hemoglobin, and therefore related to the transport of O_2, they focused on its role on cellular respiration at the mitochondrial level. Indeed, iron is a constituent of the I-IV complexes of the mitochondrial respiratory chain. In case of iron deficiency, mitochondria do not produce enough energy in the form of ATP and that this energy deficit may impact especially on cardiac tissue. In fact, cardiomyocytes are among the cells with the densest structures of mitochondria.

Furthermore, in the study by Hoes *et al*.,[14] an *in vitro* culture of cardiomyocytes, incubated with an iron chelator, lost its ability to produce ATP and reduced its contractility, regaining it after the restoration of iron cell homeostasis.

Other experiments on animal models have also shown how the provoking an iron deficiency in cardiac tissue induced heart failure. In some studies, a partial regression was obtained after the restoration of the correct iron content through the administration of IV Fe.[15]

The demonstration of the link between iron and HF was then obtained *ex-vivo* by analyzing tissue from the explanted hearts of patients with severe HF. These had both a lower iron content and an altered metabolism, as demonstrated by the reduced levels of certain enzymes involved in the citric acid cycle.[16]

A recent analysis by the BIOSTAT-CHF registry,[17] showed that the causes of iron deficiency are related both to low intake (malnutrition and fluid overload), altered availability of deposits (inflammation and CRF), and increased losses (use of antiplatelet drugs).

However, there is an even closer and characteristic link between the neuro-hormonal activation of HF and iron deficiency. In fact, increased aldosterone and norepinephrine levels reduce the expression of the transferrin receptor at heart level, directly causing tissue-level iron deficiency,[18] and there is a correlation between circulating norepinephrine and iron profile markers: patients with higher norepinephrine levels showed signs of iron deficiency.[19] These two studies suggest that there is, therefore, a closer link between iron deficiency and heart failure, making the former something more than a comorbidity.

The large amount of evidence in favor of one or more possible mechanisms would justify what has long been seen in the treatment of these patients.

In 2009, the FAIR-HF study[20] showed that correcting iron deficiency with IV FCM, regardless of anemia, improved symptoms in patients with HF and reduced ejection fraction/HFrEF (NYHA class II-III). These data were confirmed by the CONFIRM-HF study,[21] which showed that the correction of iron deficiency with FCM in patients with HF improved physical performance (measured with 6-minute walking test/6MWT) and significantly reduced the hospitalizations due to worsening HF. The meta-analysis published by Anker *et al*. in 2018[22] confirmed that the restoring of a correct iron profile in patients with

HFrEF reduces recurrent hospitalizations and cardiovascular deaths. Conversely, attempts to treat iron deficiencies with oral iron formulations have failed and, to date, there is no evidence to support this treatment strategy in this subgroup of patients.[23]

All the available data led to the inclusion of iron deficiencies as co-morbidities in the ESC 2016 guidelines on heart failure, which recommend screening and treatment in all patients with HFrEF, serum ferritin <100 or <299 and TSAT <20%, in order to improve symptoms, exercise capacity, and quality of life.[23,24] In the common clinical practice, iron deficiency should be searched immediately, and not only as a possible cause of anemia, as suggested by the algorithm shown in the Figure 1.[25]

A further topic concerns economic sustainability

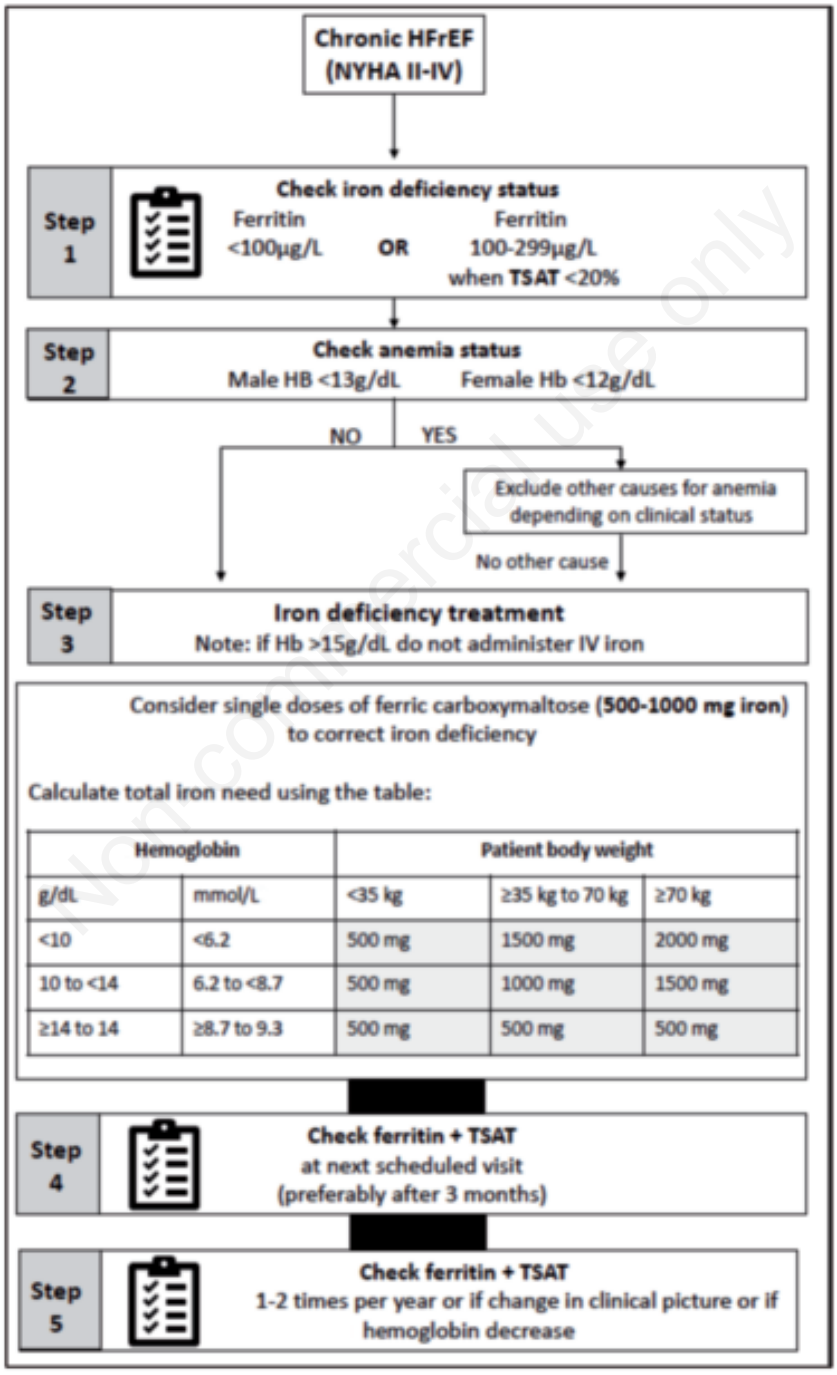

Figure 1. Scheme of screening and treatment of iron deficiency in heart failure (HF) patients. HFrEF, HF with reduced ejection fraction TSAT, transferrin saturation; Hb, hemoglobin. Modified from Lam *et al.*[25]

for the National Health System (NHS). A recent cost-effectiveness analysis has robustly demonstrated that the use of FCM in the treatment heart failure and iron deficiency would save €403 per year/patient, with an impact, if applied to the entire population of HF patients in Italy, of about €96 million per year. Such prospective simulation seems to suggest the possibility to implement a new treatment and, at the same time, thanks to the huge gains in terms of patient health, save money for the NHS.[26]

Iron deficiency anemia and chronic kidney disease

Anemia is a common complication of chronic kidney disease (CKD), occurring more frequently in patients with advanced kidney dysfunction.

Although the etiology of anemia in patients with CKD has primarily been attributed to decreased production of erythropoietin (EPO), the pathophysiology of this disease also involves an abnormal iron metabolism, partially related to excess levels of hepcidin.[27]

As CKD progresses, EPO production is decreased to a level that is inadequate to maintain a normal rate of erythropoiesis. Moreover, the elevated levels of hepcidin, commonly observed in these patients, reduce the absorption of elemental iron, the recycling of iron from senescent red blood cells by macrophages, and the mobilization of iron from the reticulo-endothelial system. Elevated hepcidin levels in patients with CKD result from both decreased renal excretion and increased production by inflammatory processes.[28]

The definition criteria of iron deficiency in patients with CKD differ from the normal population. In fact, absolute iron deficit is defined by a TSAT of less than 20%, with ferritin being less than 100 ng/mL or 200 ng/mL in non-dialysis and dialysis patients, respectively.[29] Iron functional deficiency, both due to ESA use and chronic inflammation, is characterized by a TAST lower than 20% with serum ferritin >800 ng/mL.[30]

Iron deficiency, with or without anemia, is one of the most common complications occurring in patients with CKD or undergoing dialysis. It is frequently associated to common symptoms such as asthenia, headache, dyspnea, cognitive deficit and irritability.[27]

A multicenter prospective study carried out on 755 patients with CKD at stage 3-5 showed an unexpectedly high prevalence of iron deficiency (more than 60%) in the setting of the tertiary nephrology care.[31] About 75% of patients with iron deficiency did not undergo iron supplementation, and the 35% of patients were not treated with ESA despite of Hb levels lower than 11 g/dL, highlighting a persistent clinical inertia in the anemia management, remarkable especially for iron supplementation

The uses of ESAs to target normal hemoglobin levels may be associated with adverse cardiovascular events, particularly in patients who do not achieve target hemoglobin levels despite higher doses of ESAs. A meta-regression analysis of 31 trials indicated that in patients with CKD, a higher ESA dose may be associated with all-cause mortality and cardiovascular complications that are independent of the target hemoglobin level.[32]

An intervention with ESA should achieve a population distribution centered on a mean of 11 g/dL with a range of 10-12 g/dL,[27] or not above 11.5 g/dL (115 g/L) in adult patients with CKD, as suggested by the KDIGO Work Group.[33]

However, there is a general consensus on the need to correct iron deficiency before starting ESA only if the patient does not reach the Hb target mentioned before.

Guideline recommendations show some differences: NICE suggests oral iron supplementation for patients not treated with ESA, reserving intravenous iron administration only if the oral route is not tolerated or if it does not reach the target. For patients treated with ESA, NICE recommends the administration of intravenous iron.[34]

American guidelines recommend that patients should be iron replete to achieve and maintain the target Hb, whether receiving ESAs or not, defined as ferritin >100 microgram/L (but not exceeding 800 microgram/L) and TSAT >20%. The choice between oral vs. parenteral iron depends on the severity of iron deficiency, the previous response and side effects, the availability of venous access and the need to initiate ESA therapy.[35]

The KDIGO guidelines differently recommend for adult CKD patients with anemia on ESA therapy or not, a trial of IV iron (or in CKD no-dialysis patients alternatively a 1-3 month trial of oral iron therapy) if an increase in Hb concentration without starting ESA treatment is desired, and if TSAT ≤30% and ferritin ≤500 ng/mL.[33]

The largest study on patients with CKD is the FIND-CKD study, comparing oral (iron sulphate) to intravenous FCM iron therapy with the aim of reaching a serum level of ferritin of 100-200 µg/L (low ferritin) or of 400-600 µg/L (high ferritin) in patients with anemia and iron deficiency not undergoing ESA treatment. The study pointed out that FCM was able to delay or to reduce alternative therapy of anemia with comparison with iron sulphate.[36]

A recent sub-analysis of the FAIR-HF trial showed an improvement of renal function in patients with chronic heart failure and renal dysfunction when treated with FCM.[37]

Further, Toblli *et al*. studied 30 not dialyzed subjects with CKD treated with ESA but not responsive to oral iron therapy. In this population, the shift to in-

travenous treatment with FCM was associated with an improvement in hematologic parameters and iron profile, with a significant reduction of the ESA dosage needed to maintain hemoglobin to target.[38] The administration of FCM at a dosage of 1000 mg determined a prolonged increase of hemoglobin up to 24 weeks. Conversely, the ESA dosage decreased from the first month of FCM therapy, with a reduction of 80% of the cumulative dose.

In conclusion, in patients with CKD, some aspects seem to favor intravenous over oral administration of iron. In fact, a low patient compliance due to gastrointestinal adverse effects, and a chronic inflammatory state, determining high serum levels of hepcidin, make oral iron administration less effective, namely when anemia correction should be rapid. Last but not least, the time-consuming of the oral therapy seems to be another aspect which favors intravenous iron formulation in patients with CKD.[29]

Future perspectives

At the moment, several studies on the use of IV Fe in patients with medical diseases, such as chronic obstructive pulmonary disease, diabetes mellitus and perioperative anemia, are ongoing. Certainly, all these fields represent a challenge for the daily management of anemia in an Internal Medicine environment.

However, current research is primarily focused on HF patients. In fact, at least 4 large-scale trials, involving approximately 6600 patients, are being carried out in this subgroup of patients.

The most recent published study is the AFFIRM-*AHF,* a multicenter, randomized (1:1), double-blind, placebo-controlled trial, that recruited 1100 patients hospitalized with AHF and an iron deficiency defined as serum ferritin less than 100 ng/mL, or between 100 and 299 ng/mL if transferrin saturation was <20%. Eligible patients were randomized (1:1) to intravenous FCM or placebo and received the first dose of study treatment just prior to the discharge for index hospitalization. Patients were followed-up for 52 weeks.

Total cardiovascular hospitalizations and cardiovascular deaths were lower in the FCM than placebo group (RR 0.80, 95%CI 0.64-1.00, P=0.050). The risk of heart failure hospitalizations occurred less in the FCM.

group with respect to the placebo group (RR 0.74; 95%CI 0.58-0.94, P=0.013). Finally, also the composite of first heart failure hospitalization or cardiovascular death was significantly lower in FCM group than in the placebo group (HR 0.80, 95%CI 0.66-0.98, P=0.030).[39]

A next trial, the FAID-HF2, is a randomized, parallel-group, double-blind study of patients with chronic heart failure and iron deficiency (1200 patients). The primary outcome is the combination of hospitalization and death 12 months after surgery.[40] A third study carried out on a similar (chronic heart failure and iron deficiency) but larger population (3200 patients) will have the objective of demonstrating the reduction in mortality, hospitalization and improvement in physical performance (6-minute walking distance) of this population.[41]

Finally, a fourth single-blind (outcome Assessor), parallel group, randomized open-label multicenter study using iron isomaltoside is aimed at evaluating CV mortality and hospitalization for worsening heart failure during 2.5 years of follow-up.[42]

Conclusions

As our survey data also seem to show, in Internal Medicine anemia management remains a challenge for both diagnosis and treatment. In particular, functional iron deficiency in chronic diseases need to be well known to obtain an appropriate diagnosis and thereby treatment. In the next future new data on treatment of anemia associated with HF, CKD and chronic inflammatory diseases will allow to improve the actual management of anemia in Internal Medicine.

References

1. Italian Minister of Health. Annual report on hospitalization - Year 2018; June 2019.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211-59.
3. Fonseca C, Araújo M, Moniz P, et al. Prevalence and prognostic impact of anemia and iron deficiency in patients hospitalized in an internal medicine ward: The PRO-IRON study. Eur J Haematol 2017;99:505-13.
4. Migone De Amicis M, Poggiali E, Motta I, et al. Anemia in elderly hospitalized patients: prevalence and clinical impact. Intern Emerg Med 2015;10:581-6.
5. Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. Int J Hematol 2018;107:16-30.
6. Cappellini MD, Comin-Colet J, de Francisco A et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol 2017;92:1068-78.
7. Cancelo-Hidalgo MJ, Castelo-Blanco C, Palacios S, et al. Tolerability of different oral iron supplements: a systematic review. Curr Med Res Opin 2013;29:291-303.
8. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One 2015;10:e0117383.
9. Nikravesh N, Borchard G, Hofmann H, et al. Factors influencing safety and efficacy of intravenous iron-carbo-

hydrate nanomedicines: From production to clinical practice. Nanomedicine 2020;26:102178.
10. Neiser S, Rentsch D, Dippon U, et al. Physico-chemical properties of the new generation IV iron preparations ferumoxytol, iron isomaltoside 1000 and ferric carboxymaltose. Biometals 2015;28:615-35.
11. Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. J Card Fail 2005;11:91-8.
12. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013;368:1210-9.
13. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013;165:575-82.e3.
14. Hoes MF, Grote Beverborg N, Kijlstra JD, et al. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. Eur J Heart Fail 2018;20:910-9.
15. Xu W, Barrientos T, Mao L, Rockman HA, Sauve AA, Andrews NC. Lethal cardiomyopathy in mice lacking transferrin receptor in the heart. Cell Rep 2015;13:533-45.
16. Kobak KA, Radwańska M, Dzięgała M, et al. Heart Failure Rev 2019;24:269-77.
17. van der Wal HH, Grote Beverborg N, Dickstein K, et al. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. Eur Heart J 2019;40:3616-25.
18. Maeder MT, Khammy O, dos Remedios C, Kaye DM. Myocardial and systemic iron depletion in heart failure implications for anemia accompanying heart failure. J Am Coll Cardiol 2011;58:474-80.
19. Moliner P, Enjuanes C, Tajes M, et al. Association between norepinephrine levels and abnormal iron status in patients with chronic heart failure: is iron deficiency more than a comorbidity? J Am Heart Assoc 2019;8:e010887.
20. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436-48.
21. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2015;36:657-68.
22. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalizations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail 2018;20:125-33.
23. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial [published correction appears in JAMA 2017; 317(23): 2453]. JAMA 2017;317:1958-66.
24. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.
25. Lam CSP, Doehner W, Comin-Colet J, IRON CORE Group. Iron deficiency in chronic heart failure: case-based practical guidance. ESC Heart Fail 2018;5:764-71.
26. Rognoni C, Gerzeli S. Ferric carboxymaltose for patients with heart failure and iron deficiency in Italy: cost-effectiveness and budget impact. J Comp Eff Res 2019;8:1099-110.
27. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012;23:1631-4.
28. Peters HP, Laarakkers CM, Swinkels DW, Wetzels JF. Serum hepcidin-25 levels in patients with chronic kidney disease are independent of glomerular filtration rate. Nephrol Dial Transplant 2010;25:848-53.
29. Cappellini MD, Comin-Colet J, de Francisco A, et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. Am J Hematol 2017;92:1068-78.
30. Locatelli F, Bárány P, Covic A, et al. Kidney disease: improving global outcomes guidelines on anemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrol Dial Transplant 2013;28:1346-59.
31. Minutolo R, Locatelli F, Gallieni M, et al. for the REport of COmorbidities in non-Dialysis Renal Disease Population in Italy (RECORD-IT) Study Group. Anemia management in non-dialysis chronic kidney disease (CKD) patients: a multicenter prospective study in renal clinics. Nephrol Dial Transplant 2013;28:3035-45.
32. Koulouridis I, Alfayez M, Trikalinos TA, et al. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a meta-regression analysis. Am J Kidney Dis 2013;61:44-56.
33. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279-335.
34. National Collaborating Centre for Chronic Conditions, Royal College of Physicians. Guideline on anemia management in chronic kidney disease 2015. National Institute for Clinical Excellence. Available from: http://www.nice.org.uk/guidance/NG8/evidence
35. Mikhail A, Brown C, Williams JA, et al. Renal Association Clinical Practice Guideline - anemia of chronic kidney disease. BMC Nephrol 2017;345:1-29.
36. Macdougall IC, Bock A, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anemia. Nephrol Dial Transplant 2014;29:2075-84.
37. Ponikowski P, Filippatos G, Comin Colet J, et al for the FAIR-HF Trial Investigators. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. Eur J Heart Failure 2015;17:329-39.
38. Toblli JE, Di Gennaro F. Switching patients with non-dialysis chronic kidney disease from oral iron to intravenous ferric carboxymaltose: effects on erythropoiesis-stimulating agent requirements, costs, hemoglobin and iron status. PLoS One 2015;10: 0125528.
39. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute

heart failure: a multicenter, double-blind, randomized, controlled trial Lancet. 2020;396:1895-904.
40. ClinicalTrials.gov. Intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity and mortality (FAIR-HF2). Identifier: NCT03036462.
41. ClinicalTrials.gov. Randomized placebo-controlled trial of FCM as treatment for heart failure with iron deficiency (HEART-FID). Identifier: NCT03037931.
42. ClinicalTrials.gov. Intravenous iron treatment in patients with heart failure and iron deficiency: IRONMAN (IRONMAN). Identifier: NCT02642562.