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Editorial

Use of Iron Therapy in Chronic Kidney Disease

Editorial

Anemia is a common complication in patients with chronic kidney disease (CKD), and increases with the progression of renal dysfunction [1]. The main cause of anemia is the inadequate production of erythropoietin (EPO), a glycoprotein mainly produced by the kidney responsible for the growth of erythroid cells in the bone marrow [2]. Iron deficiency is another common cause of anemia in these patients and is a major cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) [3]. Approximately, 50% of patients with CKD, who have anemia and are not receiving ESA or iron supplementation show depleted iron stores in their bone marrow [4]. Although the use of intravenous iron in hemodialysis patients has significantly increased during the last decade [5], the appropriate iron dosing strategy in CKD remains debatable.

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for anemia in CKD states first on diagnosis of iron deficiency: as liver or bone marrow biopsies are invasive and inappropriate in everyday clinical setting, nephrologists used serum ferritin and transferrin saturation (TSAT) to assess the iron status in CKD patients [6]. However, these 2 markers are not exempt from limitations, a serum ferritin level of <15 ng/ml predicts iron depletion, it is influenced by various factors such as inflammation and infection, that are often seen in CKD patients [7]. TSAT is also influenced by inflammation and nutritional status [8]. KDIGO, but also European Renal Best practice (ERBP) suggest a trial of iron therapy if an increase in hemoglobin (Hb) concentration without starting ESA treatment is desired and TSAT is ≤ 30% and serum ferritin is ≤ 500 ng/ml [9]. The guideline also states that for adult CKD patients on ESA therapy who are not receiving iron supplementation, a trial of iron therapy should be realized if an increase in Hb concentration or a decrease in ESA dose is desired and TSA is ≤ 30% and serum ferritin ≤500 ng/ml. However, methods for supplementing iron in patients with renal anemia vary widely among countries: Australia, Canada and ERBP insist on lower TSAT and ferritin levels; Japan is even more conservative in its iron prescriptions [10].

The use of iron is now a common practice in the treatment of anemia in CKD patients either oral or intravenous (IV), in spite of the concerns about the increase in ferritin levels and tissue iron overload due to the use of high/continuous iron supplementation, toxicity of different iron products, and the role of iron products in infection [11]. The decision for oral or IV iron treatment should balance the benefits and risks for the patient. Oral iron formulations are less expensive, and need high dosages (325 mg three times daily) to be effective; however at these dosages, the gastrointestinal side effects experienced by most of the patients may reduce the effect and adherence to treatment [12]. Some studies reported that IV therapy increases both Hb and ferritin, while oral iron therapy increases Hb without increasing substantially iron stores [13]. Moreover, most of the clinical studies evaluating oral and IV administration reported that IV iron therapy leads to a higher increase in Hb than oral iron therapy [14]. In some cases oral iron therapy is dedicated to non-dialysis CKD patients, but a recent trial shows some advantages to IV iron therapy in these patients [15]. In these patients the effects on kidney function remains unclear. A randomly trial was very recently published where CKD patients stage 3 and 4 and iron deficiency anemia were assigned either to oral iron or intravenous iron sucrose medications [16]. The primary outcome was the between-group difference in slope of measured glomerular filtration rate (mGFR) change over two years. The mGFR declined similarly over the study period in both treatment groups, but there were more cardiovascular events and more infections resulting in hospitalizations in the IV group resulting in an early termination of the study on the recommendation of an independent data and safety monitoring board [16]

IV iron therapy is better tolerated than oral iron therapy, has more adherence and efficacy, but requires the existence of and IV access and in Europe after the recommendations of the European Medicines Agency's Committee for Medicinal Products for Human Use, adequate measures should be taken to minimize the risk of allergic reactions [17], by correction on the summary of all intravenous iron products characteristics: they included hypersensitivity reactions that could be life-threatening, previous reaction to an iron infusion, multiple drug allergies, severe atopy and systemic inflammatory diseases [17]. IV iron therapy is preferred for patients under hemodialysis (HD), as they have a vascular access already available. Even in non-dialysis CKD patients the recently FIND-CKD study found that IV iron is superior to oral iron therapy especially when a high ferritin level is assigned, showing higher Hb levels and iron stores, as well as a higher improvement in their quality of life [18]. Routes of iron administration in CKD patients were compared in a recent systematic Cochrane review [19]. The review found significantly higher levels of Hb (mean difference 0.90 g/dL), TSAT and ferritin in patients who were treated with intravenous iron compared with

oral iron. In addition, intravenous iron administration was associated with a significant reduction in ESA dose in dialysis patients. One of the concerns in IV therapy is that the used iron doses overcomes the binding capacity of transferrin, leading to an increase in non-transferrin bound iron, with the development of oxidative stress, and iron deposition in organs [20].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) [21] showed that the number of HD patients with IV iron supplementation increased in most countries; however, and even more important, the doses prescribed to the patients also increased in the past 10-15 years. Overall, the mean serum ferritin has increased overtime, and the proportion of patients with serum ferritin ≥ 800 ng/ml has also increased [21]. The recent KDIGO controversies conference on iron management in CKD [22], recognized the entity of iron overload in HD patients. There are several studies reporting tissue iron accumulation in HD patients treated with ESAs and IV iron [23]. The recent study published by one of ours examined prospectively the iron concentration in the liver of patients undergoing HD using MRI. We found that over 80% of the patients exhibited hepatic iron overload [24]. Importantly, iron withdrawal or a major reduction in the iron dose resulted in decreased iron concentrations in the liver. The long-term effects of iron deposition in these tissues are still unclear.

In vitro studies show a relationship between the availability of iron and bacterial virulence, as iron is important for bacteria multiplication in the host. Therefore, clinical conditions associated with iron excess in the host may increase the risk for infection [25]. Clinical studies reported different results about the linkage of IV iron therapy with infection. One study observed a significantly higher rate of bacterial infection with higher frequency of dosing administration [26]. A one year follow-up study of HD patients examined the relationship between iron stores, IV iron dosing and bacteremic risk, and found that patients with higher iron stores had a significantly higher risk of bacteremia; however they did not find an IV iron dose-response relationship [27]. After the recent changes in the pattern of IV treatment [28], in a two year follow-up study of HD patients treated with IV iron, it was found a significant increase in TSAT and serum ferritin; however it was not associated with an increase in the incidence of infectious complications. An observational study that included 14,078 patients reported the possibility of infection-related mortality with higher iron doses [29]. The type of IV iron formulation might have also an impact in the rate of infection [30]. Randomized clinical trials are also needed to assess the effect of cumulative IV iron doses and the risk of infection-related morbidity and mortality.

In spite of the widespread use of IV iron supplementation in HD patients the safest dosing strategy is still poorly clarified, as well as its relation with serum ferritin levels, iron overload and mortality risk. Actually, only few studies addressed these questions and presented controversial results: three of them [31-33] found no association between high iron doses, high ferritin levels and mortality, and three of them an increased mortality among patients with higher doses of IV iron, or high ferritin levels [34-36]. Considering the controversial data in literature, there is a clear need to develop clinical trial with longer follow-up periods of HD patients to evaluate the effect of long-term cumulative IV iron doses and the impact of serum ferritin levels on all-cause and cardiovascular mortality. In accordance a clinical trial, the Proactive IV iron Therapy for Haemodialysis patients (PIVOTAL), has recently stated and the aim is to compare the effect of IV iron high-dose versus low-dose regimen on all-cause mortality, and to evaluate the incidence of non-fatal cardiovascular endpoints, in HD patients along 2-3 year follow-up [37]. Another aim of this study is to compare the effect of the two regimens on ESA requirements, red blood cell transfusions, and complications of HD treatment and quality of life of the patients.

Controversial points appeared recently on iron supplementation in CKD: the recent KDIGO guideline contributed to an increase in the frequency and in the dose of iron used to treat anemia of CKD patients. Higher values of TSAT and ferritin have been found in dialysis patients, raising concerns about iron overload. Some recent data alerts to the safety of cumulative higher doses in dialysis patients, as they seem to be linked with increased risk of iron overload, toxicity and infection. Relationship with increased risk of mortality must be clarified.

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