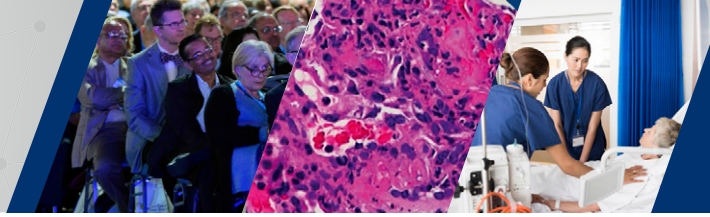

Intravenous Iron Use in the Care of Patients with Kidney Disease

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Introduction

The majority of patients with CKD suffer from iron deficiency, with many patients receiving maintenance hemodialysis being in a state of negative iron balance, such that their losses of iron from the body exceed the dietary intake and/or absorption of iron *via* the gut (1,2). The latter is mediated *via* upregulation of hepcidin activity which occurs in inflammatory states, including uremia. In general, this limits the efficacy of oral iron supplementation, which, in turn, has led to the widespread use of intravenous (IV) iron, particularly in the hemodialysis setting.

Many different IV iron preparations are available worldwide, and these differ in their physicochemical characteristics, biologic actions, and quantity of iron able to be administered at a single sitting. Some of the older IV iron preparations (iron sucrose, iron gluconate) exhibit a more rapid release of iron from the iron-carbohydrate complex, limiting the rate and dose of iron administered. This is not a problem in patients receiving maintenance hemodialysis who have ready vascular access, and are attending a dialysis center several times a week. However, patients not receiving dialysis are usually better off receiving one of the newer IV iron preparations (ferric carboxymaltose, ferumoxytol, or iron isomaltoside 1000), which allow for a larger dose of iron to be administered over a relatively short period of time, at a single sitting.

Concerns about the safety of IV iron have evolved over the years (Figure 1). Hypersensitivity reactions to IV iron, including anaphylaxis, used to be more common, particularly in the days when high-molecular-weight iron dextran was used, but are still rarely reported (3). Longer term concerns about IV iron include increased oxidative stress, increased atherogenesis, cardiovascular toxicity, immune dysfunction, and increased infections (4). More recently, there have been concerns about hypophosphatemia associated with certain preparations (notably iron polymaltose and ferric carboxymaltose), which could lead to osteomalacia in the long term (5).

The choice of IV iron preparation and the indications for use differ depending upon the stage of CKD, the patient phenotype, physician preference, and perhaps (most importantly) availability of the preparations. For example, ferumoxytol is used in the United States, but is not available in Europe, whereas iron isomaltoside 1000 is available in certain European countries, but not available in the United States.

To illustrate the use of IV iron in patients with CKD, and to highlight factors affecting which preparation to use, two brief case studies are described.

Case Studies

IV Iron in the Nondialysis Setting

A 48-year-old woman with type 2 diabetes and hypertension now has CKD stage 4 (eGFR 28 ml/min), and is increasingly tired. Her hemoglobin is 9.4 g/dl, her serum ferritin is 39 μg/L, her transferrin saturation is 18%, her C-reactive protein is 7 mg/L, she has normal B12 and folate levels, and there is no other obvious cause for her anemia.

This woman would almost certainly benefit from iron therapy, and the dilemma the physician has is whether she should receive a trial of oral iron, or go straight to IV iron.

How Would I Treat This Patient? I would prescribe 750–1000 mg of ferric carboxymaltose for this patient and would request to check her blood tests again in around 2 months. The reasons for using IV rather than oral iron are as follows (but there may be very good reasons why this practice would not be followed by all nephrologists, particularly when ferric citrate could be an option in the United States and Japan):

(1) Much greater probability of correcting the deficiency in iron supply to her bone marrow;
(2) Although the Ferinject Assessment in Patients with Iron Deficiency Anemia and Nondialysis-Dependent CKD study (6), the REVOKE study (7), and a meta-analysis (8) suggest that both oral and IV iron are likely to be effective, the hemoglobin response is likely to be greater and faster with IV iron (4 weeks for IV iron; ≥6 weeks for oral iron [6]);
(3) Avoids any concerns about poor adherence to oral iron therapy;
(4) Avoids any concerns about poor iron absorption from the gut (likely to be low in view of her current eGFR);
(5) Avoids any concerns about subjecting her to gastrointestinal side effects (experienced by 20%–30% of patients given oral iron) (9);

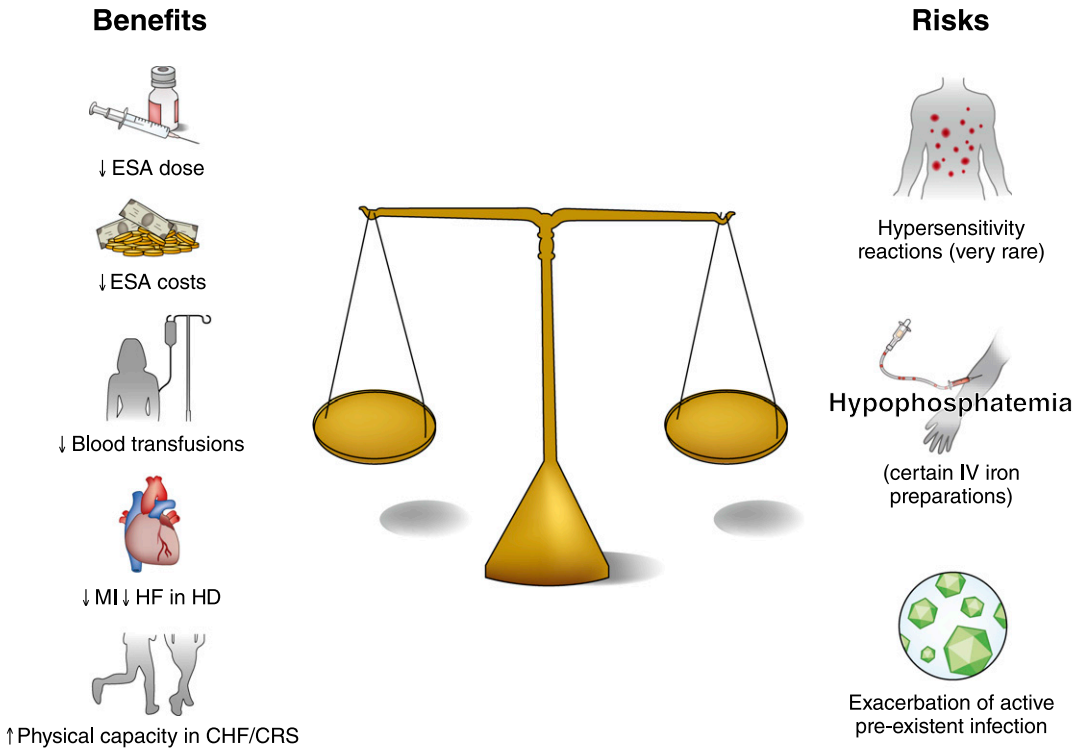

Figure 1. | **Benefits and risks of IV iron therapy in CKD.** CHF/CRS, chronic heart failure/cardiorenal syndrome; ESA, erythropoiesis-stimulating agent; HD, hemodialysis; HF, heart failure; MI, myocardial infarction.

(6) Our institution runs at least one nurse-led IV iron clinic a week, and so logistically very easy to arrange. However, the lack of facilities for IV iron administration may preclude its use over oral iron in other centers.

Why this particular IV iron preparation? No strong reason other than a greater evidence-base for ferric carboxymaltose compared with other IV iron preparations available in the United Kingdom. However, a recent randomized, controlled trial of this agent suggested a greater incidence of hypophosphatemia with ferric carboxymaltose compared with ferumoxytol (10). This could be a concern in patients at risk of osteomalacia (*e.g.*, those with inflammatory bowel disease and vitamin D deficiency) in whom repeated IV iron infusions over many years are required. In the CKD setting, however, this may be less of a concern. Alternative preparations that could be used in this setting include ferumoxytol (in the United States), low-molecular-weight iron dextran, and iron isomaltoside 1000.

IV Iron in Hemodialysis

A 32-year-old man has been on thrice-weekly hemodialysis for 3 months. His latest hemoglobin was 9.9 g/dl on 6000 U of epoetin every dialysis, his serum ferritin level was 220 μg/L, and his transferrin saturation was 20%. Since starting hemodialysis, he has been receiving intermittent IV iron sucrose (average 200 mg per month).

How Would I Treat This Patient? This is a young patient, already on a reasonable dose of epoetin, in whom I would be aiming for a hemoglobin concentration of around 11–12 g/dl. I would hope that he would be suitable for kidney transplantation, and would wish to minimize exposure to red-cell transfusions. Although his iron biomarkers are not grossly inadequate, there is a reasonable chance that he has iron-restricted erythropoiesis and could respond to additional IV iron. I would therefore manage him as per the high-dose arm of the recently published Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) study (11), and prescribe two doses of 200 mg of iron sucrose each over the first two dialysis sessions of the month. I would continue this dosing regimen, only stopping iron temporarily if his serum ferritin became significantly greater than 700 μg/L and/or his transferrin saturation became >40%. I would hope to maintain his serum ferritin level around 600 μg/L and his transferrin saturation around 25%. Given the results of the PIVOTAL study, I would hope that his dose of epoetin would decrease, his chances of requiring a blood transfusion be minimized, and his risk of cardiovascular events such as myocardial infarction and heart failure reduced. I would no longer be concerned about increasing his risk of developing infections, but would withhold IV iron should he develop any acute infective episodes (11).

Conclusions

Over the past three decades, nephrologists have been juggling with the balance between the use of erythropoiesis-stimulating agents (ESAs) and IV iron, attempting to minimize both, but recognizing that IV iron can augment the response to ESA therapy. The latest evidence from the PIVOTAL trial has not only dispelled a number of serious concerns about the use of IV iron, but has also shown

possible cardiovascular benefits, suggesting that this balance has swung in favor of using less ESA therapy and more IV iron; however, the physician would do well to heed the upper iron safety thresholds in dialysis patients imposed in the PIVOTAL trial (ferritin 700 μg/L and transferrin saturation 40%).

Disclosures

Dr. Macdougall reports grants and personal fees from Vifor Pharma, personal fees from Pharmacosmos, and grants and personal fees from AMAG, outside the submitted work.

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