Balance of Benefit and Risk in Intravenous Iron Treatment in Chronic Kidney Disease

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Summary: Iron supplementation is an important aspect of treatment for hemodialysis patients, with most administration by an intravenous route. As with any drug, decisions as to treatment are most meaningful when benefits and risks are weighed in the context of the individual patient's clinical characteristics. In this article, knowledge of benefits and risks of intravenous iron are reviewed.
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Iron deficiency is a frequent problem in patients with kidney disease. Among patients on hemodialysis, it is an expected complication resulting from procedural blood loss and other causes.[1] Most patients on hemodialysis require ongoing replacement with iron, generally administered intravenously during the dialysis treatment. It is less well known that iron deficiency also commonly is present in patients with chronic kidney disease (CKD) not on dialysis (ND). A study based on National Health and Nutrition Examination Survey program data found that approximately 60% to 80% of patients with stages 2 to 5 CKD-ND had a serum ferritin level less than 100 ng/mL or a transferrin saturation transferrin percentage saturation (TSAT) less than 20%.[2] Furthermore, Stancu et al[3] found that nearly half of stages 3 to 5 CKD-ND patients had depleted iron stores measured by bone marrow sampling. The reason for the frequency of iron deficiency in nondialysis CKD is less clear than for dialysis patients, but the implications for treatment are analogous figure 1.

The primary treatment for iron repletion in hemodialysis patients is intravenous (IV) iron, based on studies indicating that oral iron has minimal efficacy in this population and that, in contrast, IV iron is highly efficacious.[4–6] In patients on peritoneal dialysis and for patients with CKD-ND, the efficacy of iron drugs has been less well studied and in practice both oral and IV iron repletion are used. In this review we consider the efficacy of iron treatment for patients with CKD. Risks of treatment are considered and we attempt to present an approach to balancing benefits and risks that could be applied to individual patients based on their unique characteristics. The focus will be on IV iron in dialysis because of incomplete data available for other agents and settings.

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BENEFITS OF INTRAVENOUS IRON THERAPY

Before the ESA era, frequent blood transfusions and sluggish iron incorporation into red cells in the absence of erythropoietin led to frequent iron overload.[7–9] In contrast, after ESAs were introduced into practice in 1989, iron deficiency became increasingly prevalent among hemodialysis patients.[10] By 1993, severe iron deficiency was common; more than half of hemodialysis patients in the United States had a TSAT less than 20%, and more than 35% had a TSAT less than 10%.[11] This degree of prevalence and severity of iron deficiency mandated an intensive approach to iron therapy because it was clear that a basic health need of patients was not being fulfilled. At that time, the need for iron replacement shifted the fulcrum on the virtual scale on which benefits and risks are weighed in favor of IV iron use, despite the more common occurrence of hypersensitivity reactions[12] with IV iron preparations used in that era. The focus in that era was truly patient-centered: and improvement in hemoglobin level and a reduction in symptoms. In contrast, today, IV iron use has become almost universal, the mean serum ferritin level is much higher, and the primary driver is no longer patient-centered, rather it is a reduction in erythropoiesis-stimulating agent (ESA) dose requirements. Reconsideration of the balance of benefits and risks today, with absolute iron deficiency much less common, is warranted.

When evaluating the benefit of any treatment, there is a need to understand how treatment influences patient-centered outcomes. Often, such information is not available. A second line of evaluation of treatment benefit is the effect on surrogate measures that have been shown in clinical trials to be associated strongly and independently with improved patient-centered outcomes. For IV iron therapy neither level of evidence

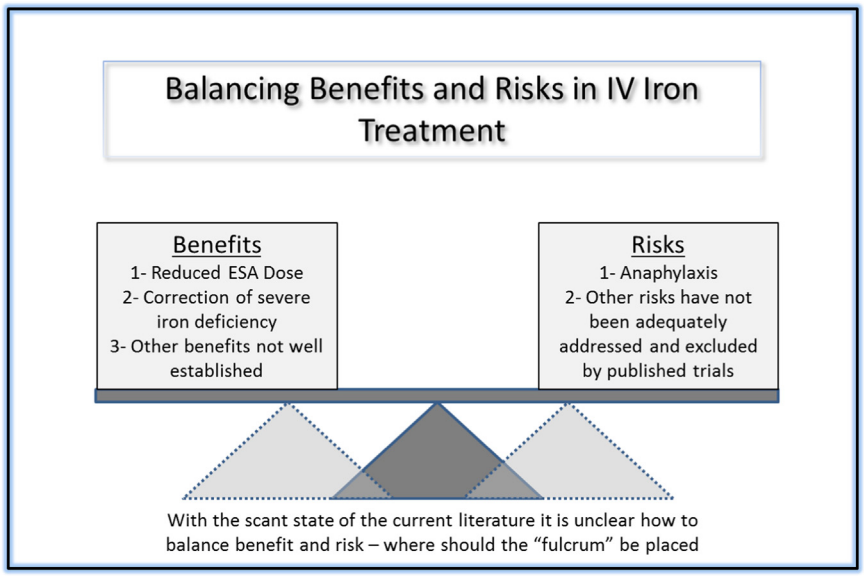

Figure 1. Balancing benefits and risks in IV Iron Treatment.

currently exists. Patient-centered outcomes such as mortality, hospitalizations, symptom relief, and quality of life have not been studied sufficiently. In contrast, there is extensive literature indicating that IV iron therapy is effective for improving certain surrogate measures (but surrogates not adequately shown to be related to improved outcomes): improved hemoglobin (Hgb) concentrations and reduced ESA dose requirements.[13]

Studies from the 1990s to 2000s found that regular administration of IV iron led to increasing Hgb levels and/or reduced ESA dose requirements.[4–6,14–16] In the early studies patients generally had relatively low levels of serum ferritin and TSAT compared with the current time period, therefore the effect of IV iron might have been magnified. A previously published study that used iron dextran administered at 200 mg/wk, induced a 46% reduction in ESA dose requirements compared with oral iron supplementation.[16] In this study the mean serum ferritin level at baseline was 191.2 ± 18.1 ng/mL in the IV iron group. The positive result generally was consistent with other subsequent studies on this subject.

The effect of IV iron on Hgb concentration in the current era, in which typical serum ferritin and TSAT levels are significantly higher, is less clear. Some relevant evidence was provided by the Dialysis Patients' Response to IV Iron with Elevated Ferritin study. In this study, treatment of IV iron was tested at higher ferritin concentrations (range, 500-1,200 ng/mL). Despite these higher levels, efficacy was shown with IV iron, improved Hgb level, and perhaps reduced ESA dose requirements.[17,18] Although the results were less robust than previous studies of patients with lower iron indices, it was a useful confirmation of a continued erythropoietic efficacy of IV iron even at higher iron levels.

Taken together, the literature consistently indicates that among patients on hemodialysis, IV iron increases Hgb level and reduces the ESA dose requirements.[13] As mentioned earlier, when studies of a treatment for improving patient outcomes are not available (as is true for IV iron), a demonstration of benefit for surrogate measures can be helpful. Indeed, increasing Hgb concentration could be beneficial because higher Hgb levels have been associated strongly and independently with improved outcomes in observational studies.[19] Unfortunately, a series of subsequent, well-powered, randomized controlled trials did not find that increasing the Hgb concentration with ESAs improved outcomes in these patients.[20–22] In fact, there appeared to be the opposite effect, an increase in mortality risk, cardiovascular events, and thrombosis, at least when targeting Hgb levels greater than 13 g/dL.[20–22] This would appear to nullify the results from observational studies and eliminate increasing Hgb as an acceptable surrogate measure for evaluating IV iron benefit. The highly related reduction in ESA dose decreases the cost of care, which is a valuable effect, but not one that accrues directly to the patient. Although there has been some speculation that higher ESA doses may be harmful to patients,[23] that literature remains controversial and inconclusive.

In summary, no direct patient benefit has been established for IV iron in dialysis patients. It is self-evident that treating severe iron deficiency not only supports erythropoiesis, but also supports the production of adenosine triphosphate and numerous other biologic systems. With mean serum ferritin levels in US hemodialysis patients close to 750 ng/mL in March