More than a Decade of Experience and Still No Consensus: Controversies in Iron Therapy

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During the past decade, the integration of recombinant human erythropoietin (EPO) and maintenance intravenous iron therapy into standard anemia management protocols has significantly altered the treatment of anemia in patients who are on hemodialysis (HD). Hemoglobin levels have increased inexorably and now average almost 12 g/dl (1). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines state that intravenous iron usually is required for the provision of optimal iron stores to maximize erythropoiesis-stimulating agent (ESA) efficiency in patients who are on dialysis (2). Intravenous iron therapy is needed in patients who are on HD because these patients experience ongoing blood (iron) losses, and oral iron fails to maintain adequate iron stores.

Efficient erythropoiesis requires both iron and erythropoietin (2). In these patients, intravenous iron improves iron and hematologic parameters, with health benefits of intravenous iron outweighing potential adverse effects. Use of maintenance iron improves patients' response to EPO therapy (3), replaces patients' ongoing iron losses, and helps to maintain patients' target hemoglobin and hematocrit ranges. These benefits of intravenous iron therapy have been achieved at storage iron levels far below those that generally were seen with transfusions in the pre-EPO era (4). However, according to Medicare claims data from the US Renal Data System, only slightly more than half of HD patients receive intravenous iron therapy at least once a month, demonstrating that although intravenous iron therapy is being administered to the majority of HD patients, it may not be used on a regular basis (5). Although the reasons for lack of "regular" intravenous iron may be many, such as concerns about iron parameters, particularly ferritin levels, it also may reflect variation in protocols among centers.

The KDOQI guidelines were a milestone in the development of effective, standardized principles for the management of anemia in patients with chronic kidney disease (CKD) (4). The KDOQI guidelines provided a framework for developing a maintenance intravenous iron protocol with sufficient flexibility in the actual dose regimen. As a result, thrice-weekly, weekly, every-other-week, or once-monthly or less frequent schedules are used to provide 25 to 125 mg/wk or 100 to 1000 mg of intravenous iron within 12 to 16 wk, depending on needs. Nevertheless, the guidelines left a number of important management questions unanswered, because of a lack of comprehensive evidence that is needed to develop particular recommendations.

The increasing prevalence of comorbid conditions in an aging population, however, has made the traditional iron indices of transferrin saturation (TSAT) and serum ferritin as measures of iron sufficiency problematic, particularly so in diagnosing functional iron deficiency (6). The latest 2006 version of the KDOQI anemia guidelines (2) in fact caution about the regular administration of iron when ferritin levels exceed 500, levels that are much lower than those previously experienced by HD patients in an era of no ESA, when transfusions were the only effective means of maintaining some functional capacity in severely anemic patients.

In this supplement, the first two articles examine in-depth the indices that are used to assess iron stores in patients with iron deficiency anemia. Serum ferritin and TSAT, widely used tests to measure iron levels, have significant sensitivity and specificity limitations in identifying patients with iron deficiency or iron excess. This is because both transferrin and ferritin are acute-phase reactants but in opposite directions, are affected by nutrition (7), and in the case of TSAT have significant diurnal variation. Wish (8) and Kalantar-Zadeh *et al.* (9) discuss the meaning of these "iron tests," specifically serum ferritin. At issue is whether we are striking the right balance between our choices for intravenous iron therapy in anemic HD patients—enhanced treatment outcomes, minimized short-term and potential long-term safety risks, and cost-effectiveness—by focusing too much on the ferritin level. As Wish (8) emphasizes, the previous upper ferritin level of 800 ng/ml (now lowered to 500) was never evidence based but merely served as a large buffer zone between the values "desired" and values of 2000 ng/ml that are associated with tissue deposition in hemochromatosis patients (4).

As reviewed by Wish (8), several studies in the past decade have evaluated additional and allegedly more accurate indices of iron status that better predict response to additional iron than the traditional ones (10,11). Although some of these markers, including the reticulocyte hemoglobin content (12) and percentage of hypochromic red cells (13), show promise for identifying iron deficiency and iron overload, none yet has the combination of accuracy, ease of use, cost-effectiveness, and widespread availability of the traditional tests. This article as

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well as the one by Kalantar-Zadeh *et al.* (9) also address the more hotly debated issue of the appropriate upper limit for serum ferritin. There is concern that the still lower guideline will deny treatment to some patients who could benefit from intravenous iron therapy, thereby increasing the health risks and the cost of health care in those whose anemia is responsive to intravenous iron even at elevated serum ferritin levels. Currently, more than half of all patients in the United States have ferritin levels >500 ng/ml. Ultimately, the physician has to make the decision in the context of the patient's clinical state.

As discussed by Kalantar-Zadeh *et al.* (9), the reports of hemochromatosis in dialysis patients from the pre-ESA era combined with possible associations of iron to infection and oxidative stress has fueled the fear of using iron, yet serum ferritin is not an iron transport molecule; it contains virtually no iron (14). As cogently discussed, moderate range of hyperferritinemia of 500 to 1200 ng/ml in HD patients seems to result from non–iron-related conditions and is associated with greater not lesser patient survival (15). When time-varying marginal structured analyses that adjust for bias by indication are used, death risk is not increased at higher doses of iron (16). In view of the availability of other markers of iron availability to the erythron, Kalantar-Zadeh *et al.* (9) raise the appropriate question of whether ferritin measurements have an appropriate role in CKD iron management. If other markers such as reticulocyte hemoglobin content, percentage of hypochromic red cells, or even hepcidin are used, then reimbursement for these studies will have to be developed.

In the third article of the supplement, Bishu and Agarwal (17) discuss the safety concerns that are associated with intravenous iron with a particular focus in patients who have CKD and are not yet on dialysis. This extension of iron use has significantly increased the considerable concern of oxidative stress and possible kidney and cardiovascular injury with intravenous iron use in such patients. Whether there are differences among the available parenteral iron preparations, dextran and nondextran, still is debated. Iron dextran does not (or does so minimally) whereas both iron sucrose and iron gluconate directly transfer iron to transferrin *in vitro* (17). Such transferrin transfer suggests the presence of free iron (measured as bleomycin-detectable iron), even if transiently, and the generation of oxidative stress. This issue is developed more fully by the last article in this symposium by Zager (18), who strongly believes that intravenous iron can be a driver of the free-radical reactions that lead to oxidative injury and adverse outcomes from infection. What is not clear is the relevance of much of the animal work to patients. The work of Agarwal *et al.* (19) clearly shows that acute injury occurs, whereas the study by Leehey *et al.* (20) could not demonstrate proteinuria or albuminuria despite generation of oxidative stress as assessed by plasma and urinary malondialdehyde. The significance of these short-term studies in CKD is unclear, although thought provoking, and clinical trials are needed to ascertain the long-term clinical significance of the observations. Unlike the dialysis patient, patients with less advanced kidney disease require fewer injections of iron. Efforts to develop effective oral agents and alternative means of delivering iron by dialysis clearly are avenues worthy of pursuit. It also is important to determine whether safety risks in patients who receive intravenous iron therapy result from intravenous iron use alone or are interactive with comorbid conditions that produce malnutrition and inflammation, features that are common among HD patients and in patients with compromised renal function (7,21).

The high cost of ESA agents and the ability of intravenous iron to overcome ESA resistance mandates that we continue to reexamine the issues and conduct properly designed trials to answer the relevant questions. For instance, does improper use of iron contribute to hemoglobin cycling? Will lower ferritin targets increase the cost of anemia management? Because intravenous iron is crucial to improving anemia management, how is it best administered? I believe that a balanced approach is needed (22) when administering intravenous iron and ESA, whether it is to HD patients, to continuous ambulatory peritoneal dialysis patients, or to those in the clinic with stages 3 through 5 kidney disease. Because of the limitations of the available iron markers, anemia management should be guided by several principles, including administering intravenous iron to improve erythropoiesis and not to attain specific levels of TSAT or serum ferritin and making treatment decisions on the basis of an evaluation of the whole patient rather than a single laboratory value. Potential concerns surrounding a very high serum ferritin level or fear of oxidative stress should not be considered as obstacles to implementing a continued intravenous iron protocol in ESRD, given that the dosages that are used for such a regimen typically are small.

Our understanding of anemia management has improved markedly with introduction of the KDOQI guidelines, but many issues still require creative research efforts and careful testing in the clinic setting. The revised 2006 guidelines suggest a wide range of studies on iron management. We should get on with it; they will have an impact on our practice.

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