HHS Public Access

Author manuscript

J Am Soc Nephrol. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

J Am Soc Nephrol. 2013 June ; 24(7): 1028–1031. doi:10.1681/ASN.2013050456.

Is Iron Maintenance Therapy Better than Load and Hold?

Connie M. Rhee, MD, MSc[1,2] and **Kamyar Kalantar-Zadeh, MD, MPH, PhD**[1,2,3]

[1]Harold Simmons Center for Kidney Disease Research & Epidemiology, Orange, CA

[2]University of California Irvine Medical Center, Orange, CA

[3]Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA

TEXT

The story of intravenous iron for anemia management in maintenance dialysis patients is one of the most fascinating, educational, and clinically relevant ones. There have been mixed data, strong opinions, and polarized views among different camps and across multiple dimensions. Nephrologists and hematologists have not yet arrived at a universal front or consensus on several core questions related to iron and anemia management in chronic kidney disease (CKD), namely: (1) Is iron deficiency a major component of anemia of CKD, and if so, to what extent and at what level of clinical significance, and upon what stage or severity of CKD? (2) Does iron therapy increase hemoglobin levels and improve outcomes in CKD patients independent of the background etiology of anemia, be it erythropoietin or iron deficiency, inflammation-related hyperhecidinemia, or other hematologic and non-hematologic conditions? (3) What is the best iron agent and what is the optimal strategy for iron therapy in non-dialysis dependent CKD versus chronic dialysis patients in terms of dose, frequency, and route (oral versus parenteral); and are there differences in outcomes if iron is administered consistently (i.e., weekly to monthly) versus sporadically, also known as bolus or repletion dosing or “load and hold” (i.e., providing a large amount of iron over a short period of time when needed)? (4) Does dialysis vascular access type (catheter versus arteriovenous shunt) or dialysis therapy modality including peritoneal versus hemodialysis and conventional versus frequent hemodialysis have any bearing on iron store status and the amount of iron loss, and hence, is dialysis modality an important determinant of iron therapy dose and frequency? (5) Does iron supplementation improve patients’ quality of life or survival, or does it impart harm by virtue of allergic reactions, oxidative stress and iron overload? Lastly, (6) what are the most reliable tests with which to assess iron status in CKD patients including conventional (serum iron, ferritin, and transferrin saturation ratio) versus more novel iron markers (content of reticulocyte hemoglobin, Zinc protoporphyrin,

Correspondence: Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology & Hypertension, University of California Irvine (UCI) School of Medicine, 101 The City Drive South, City Tower, Orange, California 92868-3217, Tel: (714) 456-5142, Fax: (714) 456-6034, kkz@uci.edu.
Reprint Request: Connie M. Rhee, MD, MSc, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology & Hypertension, University of California Irvine (UCI) School of Medicine, 101 The City Drive South, City Tower, Orange, California 92868-3217, Tel: (714) 456-5142, Fax: (714) 456-6034, crhee1@uci.edu

Potential Conflicts of Interest:
Dr. Kalantar has served as a consultant to Amgen, DaVita, Fresenius, Keryx, and Vifor.

percentage of hypochromic erythrocytes, hepcidin) versus elaborate tests (liver scan and liver and bone marrow biopsy)?

The vast knowledge gap surrounding iron therapy in many ways parallels the uncertainty relating to erythropoietin stimulating agents (ESAs). Indeed after over a quarter of a century of CKD anemia management we still lack clear consensus on whether raising hemoglobin levels with ESAs is safe,[1] and whether ESAs improve patient-centered outcomes despite the fact that 10% to 25% of the dialysis therapy budget has been expended on the purchase of ESAs over the past two decades. For many years, ESAs were frequently administered without reservation to nearly all dialysis patients without asking the same questions about safety and effectiveness that we ask about iron. Only recently did ESAs as a class receive a black box warning, with particular restrictions for CKD and cancer patients including exceptionally rigorous APPRISE program requirements. In contrast, such black box warnings have not yet been applied to the same good (or bad) old iron agents. Nonetheless, many nephrologists and hematologists appear to be consumed by “iron apprehension.”

Whereas the dose and frequency of ESAs in long-term dialysis patients are not frequently questioned, and while maintenance dosing of ESAs — usually from thrice weekly to every other week — is considered standard-of-care by practicing nephrologists, there appears to be less acceptance of iron administration in the same manner. There may be several reasons for this “iron apprehension”:[2] (1) A clinical trial performed over three decades ago in 137 iron deficient Somalians suggested that risk of infection in those who received iron therapy was almost five times higher than those who received placebo; [3] Although this historical study had a number of limitations and flaws including small sample size and less clear study design, implementation, and randomization patterns, it has maintained a strong influence on our iron therapy practices even today such that we still tend to withhold iron therapy when there is any sign of or concern for infection.[2] (2) In the pre-ESAs era, a number case reports were published about the risks and consequences of secondary hemochromatosis in anemic dialysis patients as a result of blood transfusions,[4] whereas case reports of iron overload and comparable ferritin levels ranging 5,000 to 20,000 ng/ml implicating IV iron administration are virtually non-existent. (3) Several in-vitro studies have indicated that there is an association between iron supplementation and oxidative stress in cell cultures,[5] but equivalent human data are not convincing. (4) A limited number of observational studies have indicated that there is an association between high serum ferritin and infection or mortality[6] as well as between iron administration and indices of cardiovascular disease [7] or death risk [8] in dialysis patients, although more recent studies using more sophisticated methods refuted prior associations as confounding.[9] (5) Several recent studies employing liver imaging techniques have shown evidence of iron overload in the liver among hemodialysis patients receiving ESA and IV iron,[10] but these data have rarely been confirmed by liver biopsies, nor has it been shown that liver iron in dialysis patient correlates with morbidity or mortality. Assuming that there may still be reason to “fear” IV iron therapy, one critical question that has persisted without any clear answer relates to the safest strategy of iron therapy administration. This question is of immediate importance and urgency given the recent drastic rise in IV iron therapy in the management of chronic dialysis patients in the bundled payment era, combined with the emerging and undeniable evidence that ESAs may cause more harm particularly if administered without adequate iron

stores, leading to relative thrombocytosis, platelet activation, and subsequent thromboembolic events and death.[11, 12]

In this issue of the *Journal,* Brookhart et al [13] examined a contemporary (2004–2008) cohort of approximately 120,000 hemodialysis patients from all DaVita dialysis units across the nation with 776,203 unique IV iron administrations to systematically evaluate the association between iron therapy dosing and frequency over one-month exposure periods with subsequent infectious events (including hospitalization and death) during subsequent 3-month follow-up periods. The investigators specifically compared low (≤200 mg/month) versus high IV iron dose (>200 mg/month); as well as "repletion" also known as "load and hold" iron therapy (i.e., boluses of a large amount of IV iron, such as 300 to 1,000 mg divided by 3 to 10 doses over several consecutive hemodialysis treatment sessions, usually over a short period of 1 to 3 weeks) versus "maintenance" iron therapy (i.e., every week, every other week, or every month administration of small amounts of IV iron such as 25 to 100 mg at each administration) to maintain consistent iron administration without any interruption. During the exposure period, over one-third of patients did not receive IV iron whereas 49% and 12% received maintenance and bolus therapy, respectively. Compared to the maintenance group bolus therapy was associated with 25 additional infection-related hospitalizations per 1,000 patient-years during the 3-month follow-up period, whereas maintenance iron therapy was not associated with worse outcomes compared to non-treatment.[13] Bolus iron therapy was also associated with an 11% higher death risk due to infectious diseases compared to maintenance therapy.

Whereas this rigorous study by Brookhart *et al*[13] suggests that maintenance iron supplementation in hemodialysis patients is safe and associated with fewer infection-related hospitalizations and deaths than the "load and hold" iron administration, the inherent limitations of such an observational study should be acknowledged. In particular, examining the prognostic implications of iron therapy using a non-randomized design may be fraught by confounding-by-medical-indication that is often not amenable to multivariate adjustment, even if novel and sophisticated methods are employed.[14] That the risk of bolus iron therapy was particularly largest among hemodialysis patients with a catheter or with recent infections may in fact point to residual confounding. However, in contrast to randomized controlled trials, such large-scale observational studies may allow us to examine treatments administered over longer periods of time, with more clinically relevant outcomes among populations that are more broadly generalizable.[14] At this time, these findings warrant further research about the pattern of iron therapy, and in particular whether the "load and hold" approach should be avoided, and may call for re-examination of the current guidelines on iron therapy with regards to the amount, frequency, and interval of IV iron infused and whether more accurate and non-invasive methods for monitoring iron stores should be explored.

Notwithstanding that IV iron therapy may lead to allergic reactions, oxidative stress, promotion of bacterial growth, and impairment of host defenses, the decade old "iron apprehension" among providers in the absence of convincing evidence has become a major handicap in the management of anemia in dialysis patients. The findings by Brookhart *et al* are inconsistent with the notion that maintenance IV iron is deleterious by enhancing

predisposition to infection or death. Many reports concerning adverse effects of iron in CKD patients are based on *in vitro* studies[5] without in vivo verification. The belief that gentle iron maintenance therapy causes more harm than the enormous underlying comorbidities of uremic patients is likely flawed, and may be analogous to fearing harm from the long-term risk of diabetes in a patient with short-term life-expectancy due to advanced metastatic cancer. Historically seen, despite sporadic reports of a possible associations between high iron marker levels and poor cardiovascular outcome in the general population,[15] more robust epidemiologic studies did not show an increased risk of coronary heart disease with high iron saturation ratios, but to the contrary showed a possible association between iron deficiency with all-cause and cardiovascular mortality in the general population.[16] Similarly, recent studies in dialysis patients showed that a low, rather than a high, serum iron level is associated with higher death risk.[17] To date no randomized controlled studies have been conducted to substantiate the risk of increased infection or death as a result of IV iron therapy in dialysis patients. Indeed, evidence indicates that the activity of the pro-inflammatory cytokine TNF-α can be reduced by IV iron therapy in CKD patients.[18]

Human bone marrow can be likened to a factory of hemoglobin production; it needs both iron as the raw material and ESA as the labor force. Providing one without the other does not allow for smooth and consistent hemoglobin production, and may indeed cause harm when both excess iron accumulates and when laborers lack sufficient raw material to work with. Sporadically overloading the labor workers with huge amounts of raw material and then withholding the supply for long intervals does not allow the dysfunctional factory to operate better. The most reasonable approach may be achieved by maintenance therapy, in which we recommend weekly, every other week or at a minimum once per month administration of IV iron, at 25 mg to 100 mg per dose, to any infection-free hemodialysis patient who receives maintenance ESA therapy and whose serum ferritin is below 1200 ng/ml.

Acknowledgments

Funding Source:

CMR is supported by an NIH/NIDDK grant (F32 DK093201). KKZ is supported by research grants from the NIH/NIDDK (R01-DK078106, K24-DK091419), and a philanthropist grant from Mr. Harold Simmons.

References

1. Kalantar-Zadeh K, Streja E, Miller JE, Nissenson AR. Intravenous iron versus erythropoiesis-stimulating agents: Friends or foes in treating chronic kidney disease anemia? Adv Chronic Kidney Dis. 2009; 16:143–151. [PubMed: 19233073]
2. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: To measure it or not to measure it in chronic kidney disease? Clin J Am Soc Neph. 2006; 1(supplement):S9–S18.
3. Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. Br Med J. 1978; 2:1113–1115. [PubMed: 361162]
4. Waterlot Y, Cantinieaux B, Hariga-Muller C, De Maertelaere-Laurent E, Vanherweghem JL, Fondu P. Impaired phagocytic activity of neutrophils in patients receiving haemodialysis: The critical role of iron overload. Br Med J (Clin Res Ed). 1985; 291:501–504.

5. Zager RA, Johnson AC, Hanson SY, Wasse H. Parenteral iron formulations: A comparative toxicologic analysis and mechanisms of cell injury. Am J Kidney Dis. 2002; 40:90–103. [PubMed: 12087566]

6. Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH. Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. Am J Kidney Dis. 2001; 37:564–572. [PubMed: 11228181]

7. Drueke T, Witko-Sarsat V, Massy Z, Descamps-Latscha B, Guerin AP, Marchais SJ, Gausson V, London GM. Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. Circulation. 2002; 106:2212–2217. [PubMed: 12390950]

8. Feldman HI, Santanna J, Guo W, Furst H, Franklin E, Joffe M, Marcus S, Faich G. Iron administration and clinical outcomes in hemodialysis patients. J Am Soc Nephrol. 2002; 13:734–744. [PubMed: 11856779]

9. Feldman HI, Joffe M, Robinson B, Knauss J, Cizman B, Guo W, Franklin-Becker E, Faich G. Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol. 2004; 15:1623–1632. [PubMed: 15153574]

10. Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, Roy M, Machado G, Janklewicz P, Drahi G, Dahan H, Cohen Y. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: A mri study. Am J Med. 2012; 125:991–999. e991. [PubMed: 22998881]

11. Keung YK, Owen J. Iron deficiency and thrombosis: Literature review. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2004; 10:387–391. [PubMed: 15497026]

12. Streja E, Kovesdy CP, Greenland S, Kopple JD, McAllister CJ, Nissenson AR, Kalantar-Zadeh K. Erythropoietin, iron depletion, and relative thrombocytosis: A possible explanation for hemoglobin-survival paradox in hemodialysis. Am J Kidney Dis. 2008; 52:727–736. [PubMed: 18760517]

13. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Intravenous iron supplementation practices and infection risk in hemodialysis patients. J Am Soc Neph. 2013 *[in press].

14. Kovesdy CP, Kalantar-Zadeh K. Observational studies versus randomized controlled trials: Avenues to causal inference in nephrology. Adv Chronic Kidney Dis. 2012; 19:11–18. [PubMed: 22364796]

15. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern finnish men. Circulation. 1992; 86:803–811. [PubMed: 1516192]

16. Sempos CT, Looker AC, Gillum RF, Makuc DM. Body iron stores and the risk of coronary heart disease. N Engl J Med. 1994; 330:1119–1124. [PubMed: 7993405]

17. Kalantar-Zadeh K, McAllister CJ, Lehn RS, Liu E, Kopple JD. A low serum iron level is a predictor of poor outcome in hemodialysis patients. Am J Kidney Dis. 2004; 43:671–684. [PubMed: 15042544]

18. Weiss G, Meusburger E, Radacher G, Garimorth K, Neyer U, Mayer G. Effect of iron treatment on circulating cytokine levels in esrd patients receiving recombinant human erythropoietin. Kidney Int. 2003; 64:572–578. [PubMed: 12846752]