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What are the considerations in balancing benefits and risks in Iron treatment?:

Balancing Benefits and Safety with Intravenous Iron Treatment

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Anemia is a common comorbidity among patients with end-stage renal disease (ESRD) that has been associated increased morbidity, mortality, and risk of hospitalization.[1] For more than 25 years, the anemia of ESRD has been managed through administration of erythropoiesis stimulating agents (ESAs), mostly epoetin alpha, supplemented with intravenous (IV) iron or, less effectively, oral iron. However, concerns about the cardiovascular safety of ESAs coupled with changes in the reimbursement policies in Medicare's ESRD program, have led to less use of ESAs and correspondingly greater use of IV iron.[2,3] As a result, average ferritin levels in the US hemodialysis population increased nearly 50% from 2009 to 2012.[4] The changing landscape of anemia management has stimulated interest in optimal use of IV iron in patients on hemodialysis.

The benefits of IV iron are reviewed in an accompanying commentary by Wish. Treatment with IV iron can correct iron deficiency, lower ESA requirements, and improve hemoglobin levels.[5] Although there had been little evidence connecting iron use to any patient-centered benefits,[6] recent work from our group found that more aggressive use of iron was associated with increases in various aspects of quality of life among patients with persistently low hemoglobin.[7]

Despite its effectiveness and widespread use, safety concerns related to the use of IV iron have persisted. IV iron bypasses the various mechanisms that keep iron metabolism tightly controlled. Common doses of IV iron, up to 125 mg per dialysis session, may overwhelm pathways that typically recycle 2–4 mg daily. Frequent administration of iron may lead to oversaturation of transferrin and the release of unbound, catalytically active iron into circulation.[8] Because iron is essential for bacterial growth, infection risk has been a longstanding concern related to iron use in hemodialysis patients. Free iron is also a potent oxidizing agent that can catalyze the formation of highly reactive oxygen species.[9,10] These

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could give rise to lipid radicals, possibly increasing the long-term risk of cardiovascular events.[11,12] Hypersensitivity reactions have also been a concern particularly with the use of the older intravenous iron formulations.[13]

Unfortunately, existing randomized controlled trials (RCTs) provide little information about the long-term safety of IV iron in hemodialysis patients as the studies have been small and of short duration.[14] Until results from larger RCTs are available, evidence about the safety of IV iron in hemodialysis patients must come from well-conducted non-experimental studies. Recently such studies have been used to assess anaphylaxis risk associated with the different iron formulations. In a very large cohort study, Wang et al found lower risks associated with the newer formulations compared with iron dextran.[15]

Several other large observational studies have focused on the cumulative effect of long-term exposure to iron. Such studies have attempted to estimate the consequences of contrasting levels of exposure such as, “How would risk of mortality differ if the entire patient population were to receive 3 g of iron versus no iron over a 6-month period?” While cumulative effects are of scientific interest, valid estimates are challenging to obtain as iron treatment decisions in routine care are driven strongly by evolving measures of hemoglobin and iron status, concomitant ESA treatment, and other clinical events. As a result, cumulative exposure is tightly entangled with many other factors that may be independently related to outcomes of interest.[16]

It is also worth noting that data on cumulative exposure effects do not align with short term treatment decisions that physicians make regarding the use of iron.[17] Indeed it is not feasible to study the effect of long-term cumulative exposure, even in a RCT, as long-term exposure could not be randomized. Physicians can only make decisions about short-term courses of treatment; they need to know when to provide iron, how much to provide, and when to avoid using iron.

In typical practice, IV iron is either provided intermittently via large repletion doses over consecutive dialysis sessions (often termed “bolus dosing”) or via small doses provided every 1 to 2 weeks to maintain iron stores (often termed “maintenance dosing”). In most dialysis units, decisions about which dosing approach to adopt are largely driven by protocols that recommend standard courses of treatment aimed at achieving target levels of hemoglobin, ferritin and transferrin saturation (TSAT).

Some recent work from our group has attempted to evaluate the short-term benefits and risks of commonly used iron dosing approaches across a variety of clinical subgroups. In a large population of hemodialysis patients, we identified short-term benefits of bolus iron administration on hemoglobin levels and iron status relative to more conservative maintenance dosing.[18] Our results were compatible with those observed in the DRIVE trial.[19] In subsequent studies, we did not observe any cardiovascular risks associated with the use of iron;[20,21] however, we did observe a modestly increased risk of infection associated with bolus dosing among patients with a history of infection and those with a central venous hemodialysis catheter.[21,22] Two other recent observational studies have reported associations between cumulative iron exposure and infection-related death and

hospitalization; however these studies were not large enough to resolve the question of whether there are clinically meaningful effects of iron exposure on these outcomes.[23,24]

In light of our recent work and the results from the DRIVE trial,[19] it is our opinion that bolus dosing may be a preferred strategy for patients with persistently low hemoglobin who have not responded well to ESAs. In these patients, more aggressive use of iron is likely to reduce ESA requirements, raise hemoglobin, and normalize iron indices. However, given the available evidence, it is our opinion that bolus dosing be used cautiously (or not at all) in patients at high risk of infection, such as those with a central venous catheter. In remaining patients, it seems reasonable to adopt a conservative approach to IV iron administration, providing small, intermittent doses sufficient to maintain iron repletion. Clearly, further research is needed to assess the long-term safety and effectiveness of different iron protocols, with the goal of identifying more individualized protocols that can maximize the known benefits of IV iron, while avoiding its potential risks.

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References

1. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. J Am Soc Nephrol. 2001; 12(11):2465–2473. [PubMed: 11675424]
2. Freburger JK, Ng LJ, Bradbury BD, Kshirsagar AV, Brookhart MA. Changing patterns of anemia management in US hemodialysis patients. Am J. Med. 2012; 125(9):906–914. e909. [PubMed: 22938926]
3. Miskulin DC, Zhou J, Tangri N, et al. Trends in anemia management in US hemodialysis patients 2004–2010. BMC nephrology. 2013; 14:264. [PubMed: 24289058]
4. Karaboyas A, Zee J, Morgenstern H, et al. Understanding the Recent Increase in Ferritin Levels in United States Dialysis Patients: Potential Impact of Changes in Intravenous Iron and Erythropoiesis-Stimulating Agent Dosing. Clin J Am Soc Nephrol. 2015; 10(10):1814–1821. [PubMed: 26286925]
5. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database Syst. Rev. 2012; 1:CD007857. [PubMed: 22258974]
6. Fishbane S. Balance of Benefit and Risk in Intravenous Iron Treatment in Chronic Kidney Disease. Semin Nephrol. 2016; 36(2):119–123. [PubMed: 27236133]
7. Freburger JK, Ellis AR, Wang L, et al. Comparative Effectiveness of Iron and Erythropoiesis-Stimulating Agent Dosing on Health-Related Quality of Life in Patients Receiving Hemodialysis. Am J Kidney. Dis. 2016; 67(2):271–282. [PubMed: 26508682]

8. Parkkinen J, von Bonsdorff L, Peltonen S, Gronhagen-Riska C, Rosenlof K. Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. Nephrol Dial Transplant. 2000; 15(11):1827–1834. [PubMed: 11071973]
9. Halliwell B, Gutteridge JM. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J. 1984; 219(1):1–14. [PubMed: 6326753]
10. Martin-Malo A, Merino A, Carracedo J, et al. Effects of intravenous iron on mononuclear cells during the haemodialysis session. Nephrol Dial Transplant. 2011
11. Brewster UC. Intravenous iron therapy in end-stage renal disease. Semin Dial. 2006; 19(4):285–290. [PubMed: 16893405]
12. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney. Int. 2002; 62(5):1524–1538. [PubMed: 12371953]
13. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. Nephrol Dial Transplant. 2004; 19(6):1571–1575. [PubMed: 15150356]
14. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. Am J Kidney. Dis. 2016
15. Wang C, Graham DJ, Kane RC, et al. Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products. JAMA. 2015; 314(19):2062–2068. [PubMed: 26575062]
16. Bradbury BD, Brookhart MA, Winkelmayer WC, et al. Evolving statistical methods to facilitate evaluation of the causal association between erythropoiesis-stimulating agent dose and mortality in nonexperimental research: strengths and limitations. Am J Kidney. Dis. 2009; 54(3):554–560. [PubMed: 19592144]
17. Brookhart MA. Counterpoint: The Treatment Decision Design. Am J Epidemiol. 2015; 182(10): 840–845. [PubMed: 26507307]
18. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA. The comparative short-term effectiveness of iron dosing and formulations in US hemodialysis patients. Am J. Med. 2013; 126(6):541, e541–e541, e514.
19. Coyne DW, Kapoian T, Suki W, et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol. 2007; 18(3):975–984. [PubMed: 17267740]
20. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA. Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. PLoS. One. 2013; 8(11):e78930. [PubMed: 24223866]
21. Freburger JK, Ellis AR, Kshirsagar AV, Wang L, Brookhart MA. Comparative short-term safety of bolus versus maintenance iron dosing in hemodialysis patients: a replication study. BMC nephrology. 2014; 15:154. [PubMed: 25245951]
22. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection Risk with Bolus versus Maintenance Iron Supplementation in Hemodialysis Patients. J Am Soc Nephrol. 2013; 24(7):1151–1158. [PubMed: 23787911]
23. Miskulin DC, Tangri N, Bandeen-Roche K, et al. Intravenous iron exposure and mortality in patients on hemodialysis. Clin J Am Soc Nephrol. 2014; 9(11):1930–1939. [PubMed: 25318751]
24. Tangri N, Miskulin DC, Zhou J, et al. Effect of intravenous iron use on hospitalizations in patients undergoing hemodialysis: a comparative effectiveness analysis from the DEcIDE-ESRD study. Nephrol Dial Transplant. 2015; 30(4):667–675. [PubMed: 25366328]