

It's Time to Compare Anemia Management Strategies in Hemodialysis

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Randomized trials of intravenous (IV) iron have repeatedly demonstrated a rise in hemoglobin (Hgb), an erythropoiesis-stimulating agent (ESA) dose-sparing effect, and apparent safety. Such benefits were confirmed in a trial in hemodialysis patients with high ferritin receiving high ESA doses. But long-term randomized safety trials of IV iron have not been performed, which critics blame on IV iron manufacturers, leading some to question widespread use of IV iron to optimize Hgb and reduce ESA dose. ESAs increase risks of cardiovascular events and death when used to target higher *versus* lower Hgb values. Association studies report increasing risk with higher ESA doses at approved Hgb targets. Nevertheless, ESAs remain essential in dialysis practice. After early termination of the Normal Hematocrit Trial in 1996, analysis suggested IV iron was a risk factor for harm. In 2006, dangers related to ESA use were recognized. Trial results demonstrating IV iron was efficacious and ESA-sparing even at higher serum ferritin have intensified the focus on iron safety. Two principal alternatives in the management of anemia among dialysis patients are: (1) more intensive ESA dosing sparing iron dosing and (2) more intensive iron dosing sparing ESA dosing. Extended safety trials of IV iron *versus* no iron will become confounded by ESA dose differences between arms. Similarly higher ESA doses are associated with increased mortality risk, but trials comparing ESA doses will be confounded by Hgb differences. Rather than focus on individual products, we should perform trials comparing anemia management strategies to assess safety, efficacy, and cost.

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Anemia management in dialysis remains a contentious field (1,2). Trials of IV iron in dialysis routinely show erythropoiesis-stimulating agent (ESA) dose reductions of 30% to 70% (2). After early termination of the Normal Hematocrit Cardiac Trial (NHT) in 1996, which showed higher hemoglobin (Hgb) targets increased mortality, a *post hoc* analysis indicated higher intravenous (IV) iron dose was a risk factor for death (3). A decade later, the dangers of ESAs became apparent (4–6). Higher Hgb targets require higher ESA doses, and those not achieving target Hgb receive increasing ESA doses (3,5,7–9). Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and the NHT show ESA hyporesponders are at increased risk of CV events and death (3,5). Thus, harm associated with more intensive ESA dosing may be due to higher Hgb, higher ESA doses, or both (10,11).

A recent commentary (1) stated IV iron's safety is unproven, and we have learned little from Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE; a 6-week randomized trial of IV iron *versus* no iron) (7) or DRIVE II (the 6-week follow-up where anemia management was at the physicians' discretion) (12) while neglecting decades of other IV iron studies. Numerous studies have explored the safety of IV iron and have shown general safety in usual clinical practice (13–20).

However, no prospective safety trials of IV iron have been adequately powered to examine infections, cardiovascular events, and deaths. Compared with no iron, use of IV iron increases Hgb and/or reduces ESA dose (2). Consequently, a long-term IV iron safety trial targeting a single Hgb target will result in significantly different mean ESA doses between arms, effectively testing the safety of higher *versus* lower ESA doses as well. Therefore, I believe we should pursue trials comparing anemia practices, not individual drugs.

A number of randomized trials and observational studies have found a low incidence of acute reactions to IV iron products (14,17,19,21–23). Longer prospective observations have not clearly identified safety issues (15–17). A cohort study of U.S. dialysis patients showed those billed for >10 vials of IV iron dextran (>1000 mg) over 6 months had an elevated rate of death (adjusted relative risk: 1.11; 95% confidence interval: 1.00 to 1.24) (24). A subsequent cohort study applied "multivariable models that appropriately account for time-varying measures of iron administration as well as other fixed and time-varying measures of morbidity" and "found no statistically significant association between any level of iron administration and mortality" (25). Thus, associations between iron administration and higher mortality may be confounded (25). A meta-analysis of 13 trials comparing IV to oral iron found a greater increase in Hgb with IV iron, and no difference in mortality in the five trials reporting the data (relative risk: 0.28; 95% confidence interval: 0.02 to 5.22) (26). IV iron is hypothesized to increase infection risk, although trials have not found an increased infection rate and observational data are contradictory (27). Some hypothe-

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size that IV iron may contribute to cardiovascular events by increasing oxidative stress (28–30). Although markers of oxidative stress may be increased by iron, observational studies have been contradictory in linking IV iron use to adverse clinical outcomes (27). At usual clinical doses, the dangers of IV iron remain unproven.

The NHT, the first clear study showing ESAs might cause cardiovascular events, was terminated in 1996 because the high-Hgb target arm was approaching significant harm (3). The 1998 publication speculated the increased deaths and myocardial infarctions in the high-Hgb arm were due to lower Kt/V or IV iron but not ESA, yet the patients at highest risk were those randomized to ESA increases and not achieving the high Hgb target (3). Ten years later, the second publication from the NHT was a letter to the *New England Journal of Medicine* stating the 1998 publication presented interim results (31). The final results showed a larger treated population and longer treatment duration. The relative risk of death or nonfatal myocardial infarction was 1.28 in the high-Hgb target arm, with unadjusted confidence intervals of 1.06 to 1.56, and 0.92 to 1.78 when adjusted for the previous interim analyses (31,32). Subsequent ESA trials in various disease states show an increase in thrombosis, strokes, cardiovascular events, cancer progression, and deaths (4,6). IV iron is not accounting for ESA harm: few patients in CHOIR received iron, and their outcomes were quite good (5,8). A reanalysis of CHOIR found subjects who received high doses of ESA and subjects who were ESA hyporesponders (*i.e.* not achieving Hgb target) are at greatest risk (8). In the NHT, ESA dose was not associated with increased risk, whereas ESA hyporesponsiveness and high cumulative ESA dose were associated with increased risk (3,32). The risks associated with higher doses of ESAs operate through uncertain mechanisms and may relate to higher Hgb, ESA dose, or both. Targeting a lower Hgb may avoid the risks of ESAs in dialysis if that risk is mediated by a Hgb level >13 g/dl.

Why Is There No Long-Term Iron Safety Study?

A long-term randomized IV iron safety study is more complicated than it appears. Only hemodialysis patients receive repeated iron, so the study should be in this population, and target Hgb should be the same in both arms. To maximize any safety differences, one group should be kept very iron replete (transferrin saturation [TSAT] 25% to 50%, ferritin >500 ng/ml, receiving continuous IV iron), whereas the no-iron group would get iron only when definitely deficient (TSAT <20% or ferritin <200 ng/dl per the Kidney Disease Outcomes Quality Initiative), and then just enough to raise TSAT or ferritin above these limits. This no-iron group could also receive IV iron when ESA dose was maximized (Centers for Medicare & Medicaid Services reimburses for approximately 30,000 units of epoetin per treatment). Because studies have repeatedly shown the ESA-sparing effects of IV iron, an iron safety study will quickly evolve into “higher ESA dose without iron” *versus* “lower ESA dose with iron.”

In such a trial, the “lower ESA dose with iron” arm may perform better because compared with ESA therapy alone, addition of IV iron significantly increases mean Hgb, the pro-

portion of patients responding, the speed of Hgb response, TSAT, ferritin, and serum iron, and it decreases mean ESA dose (7,12). All of these interim outcomes and markers are associated with better survival. Additionally, some interpret the NHT and CHOIR trial results to indicate less ESA is safer than more ESA (3,5,33).

Conversely, the “higher ESA dose without iron” arm may provide greater safety. In addition to the proposed increased risk of infections and oxidative stress mentioned above, IV iron use in ESA-treated patients is associated with greater likelihood of exceeding target Hgb, which may be a mediator of the harm associated with higher dosing of ESA (34). Last, both management strategies may be equally safe, in which case the optimal management of patients should be performed on the basis of cost effectiveness.

We Still Need Anemia Trials

Safer anemia management begins with a lower Hgb target, which should be 10 to 12 g/dl, as the Food and Drug Administration recommends (4). There is sufficient controversy about the safety of IV iron and higher ESA doses to justify comparative trials of anemia management strategies. ESA producers should fund these trials because they profit the most from anemia management at this time. U.S. taxpayers have paid enough for anemia management in dialysis and should not fund these trials.

In conclusion, rather than focusing on individual drug safety, the renal community should pursue comparative trials of different anemia treatment strategies to define the most effective, safe, and cost-efficient management.

Disclosures

D.W.C. is a consultant and speaker for Watson, AMAG, and Sanofi, all makers of IV iron products. He is a past consultant to Amgen and Roche, makers of ESAs. He participates in multicenter studies of IV iron and ESAs funded by Affymax, AMAG, Amgen, Johnson & Johnson, Roche, and Watson. He is the lead investigator of the DRIVE trials.

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