Post-PIVOTAL Iron Dosing with Maintenance Hemodialysis

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Introduction

The cornerstone of anemia management in hemodialysis (HD) involves the administration of iron and erythropoietin stimulating agents (ESAs) to minimize transfusions and improve quality of life. Although there is high-quality evidence regarding ESA utilization and hemoglobin targets in patients on HD, uncertainty remained regarding the optimal use of iron. In this review, we discuss the use of iron in patients on maintenance HD with a focus on safety given the recent publication of the Proactive Intravenous Iron Therapy in Haemodialysis Patients (PIVOTAL) trial.

Iron Balance in HD

Iron balance in patients on HD is a complex process (1). Patients on HD are at risk of absolute iron deficiency and require approximately 1–2 g of supplemental iron per year due to reduced dietary intake, impaired absorption, occult gastrointestinal bleeding, frequent procedures, and laboratory testing as well as losses from dialyzer clotting and vascular access. However, iron requirements are variable, and an individualized approach to replacement is necessary. Functional iron deficiency is also common due to inflammation and the upregulation of hepcidin leading to sequestration of iron and a reduced availability for erythropoiesis.

Assessing iron status in patients on HD can be challenging. Traditional markers, such as ferritin and transferrin, have limitations in accuracy in predicting bone marrow iron stores and responsiveness to iron supplementation due to interference by malnutrition and inflammation. Thresholds for iron deficiency in HD are higher than in the general population and CKD, with a ferritin cutoff of 200 μg/L and a transferrin saturation (TSAT) cutoff of 20%. However, individuals with seemingly adequate iron stores can still have an erythropoietic response to iron administration (2). Novel markers of total body iron (the percentage of hypochromic red blood cells, reticulocyte hemoglobin content, and hepcidin) are limited by their performance and availability. Thus, ferritin and TSAT remain the most widely used markers of iron status to guide clinical decision making regarding iron administration.

Intravenous (IV) iron is an effective way to replace iron and has been shown to be superior to oral iron in the setting of HD. There are many different formulations of IV iron, each with its own pharmacokinetics and hypersensitivity profile. IV iron improves ESA responsiveness and decreases ESA requirements. In 2007, Coyne *et al.* (3) published the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study, an open-labeled, randomized, controlled trial (RCT) of 134 patients on prevalent HD and epoetin with ferritin 500–1200 ng/ml, TSAT≤25%, and hemoglobin ≤11.0 g/dl. Participants were randomized to ferric gluconate 1 g IV in eight consecutive 125-mg doses (n=66) or no iron (n=68) with a 25% increase in baseline ESA dose. The baseline ferritin in both groups was 761 ng/ml (189), TSAT was 18.6% (4.3), and hemoglobin was 10.3 g/dl (0.8). The primary outcome of change from baseline hemoglobin to 6 weeks was significantly higher in the IV iron group than in the control group by 0.5 g/dl (95% confidence interval [95% CI], 0.1 to 1.0 g/dl; P=0.03), with no significant differences in adverse events. The final ferritin and TSAT values in the IV iron group were 934 ng/ml and 25.9%. Subsequently, the DRIVE-2 study (4), a 6-week observational study following the DRIVE study in which 112 participants resumed routine anemia management, showed that participants in the IV iron group required significantly lower epoetin doses compared with their DRIVE study doses (−7527 [18,021] IU/wk; P=0.003), where epoetin doses were unchanged in the control group (P=0.81; P=0.02 for between-group comparisons). Again, there were no differences in serious adverse events between groups, but a *post hoc* analysis of both studies showed an incidence rate ratio of 0.58 in the IV iron group compared with the control group. Together, the DRIVE studies provided RCT-level evidence for the short to intermediate use of IV iron in maintenance HD.

The Long-Term Safety of Iron in HD

There has been a recent increase in IV iron utilization as clinicians attempt to limit both exposure to ESAs and their associated costs (particularly in the era of the dialysis payment bundle), which has resulted in mean iron indices drifting upward. This has caused concern, because there is a strong biologic rationale for why too much iron might be harmful for patients on HD, but data from epidemiologic studies often show an absence of risk.

Iron has negative effects on the immune system, and excess free iron can promote oxidative stress,

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leading to cellular dysfunction that was previously thought be harmful from a cardiovascular perspective. Excess iron can also accumulate in tissues, leading to iron overload. The majority of contemporary patients on dialysis treated with ESAs have evidence of hepatic iron overload as measured by magnetic resonance imaging liver iron content, with ferritin correlating with liver iron content. Optimal ferritin cutoffs to diagnose mild iron overload and severe iron overload are 160 and 290 μg/L, respectively, which are conservative in the current climate of iron utilization in HD (5). However, the clinical significance of iron overload beyond imaging abnormalities and its effect on other organs (myocardium, endocrine, and joints) are unclear but depend on the rate of iron accumulation, its magnitude, comorbidities, and life expectancy. End organ damage remains a concern for most clinicians, despite not being firmly established in any long-term cohort study.

We recently performed a meta-analysis (6) comparing the safety of high-dose IV iron (>200–400 mg/mo in most studies) with that of low-dose iron (IV or oral) in >140,000 patients on HD. In seven RCTs, there was no difference in mortality or infection, and in 15 observational studies, there was no difference in mortality, infection, or cardiovascular events. However, in the seven RCTs, only two compared higher IV iron with lower IV iron, and only two compared IV iron with no iron. In the absence of individual patient–level data, metaregression to identify thresholds for harm was not performed. An observational study showed that bolus iron administration is associated with an increased risk of infection compared with maintenance dosing in patients on HD, presumably due to additional accessing of vascular catheters (7).

The PIVOTAL Trial

The PIVOTAL trial (8) was an open-labelled, noninferiority RCT of 2141 patients on HD with ferritin <400 μg/L and TSAT<30% receiving an ESA. Participants were randomized to a strategy of proactive high-dose IV iron sucrose 400 mg every month (with a safety cutoff of ferritin =700 μg/L or TSAT=40%) or reactive low-dose IV iron sucrose 0–400 mg (targeting a minimum ferritin of 200 μg/L and TSAT of 20%), both targeting a hemoglobin of 10–12 g/dl with a median follow-up of 2.1 years. The baseline ferritin values were 214 μg/L (132–305) and 217 μg/L (137–301), respectively, and TSATs were 20% (16–24) and 20% (16–24), respectively. The median monthly dose of iron was 264 mg (interquartile range [IQR], 200–336) versus 145 mg (IQR, 100–190), with a median difference of 121 mg (95% CI, 114 to 129).

The high-dose IV iron approach was noninferior with regard to the time to the primary composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization, or death (and it was subsequently shown to be superior with adjudicated outcomes rather than investigator-reported outcomes [9]). High-dose IV iron was also superior to low-dose IV iron when considering recurrent events. Hazard ratios for death, hospitalization for heart failure, and blood transfusions were 0.66 (95% CI, 0.47 to 0.93), 0.84 (95% CI, 0.71 to 1.00), and 0.79 (95% CI, 0.65 to 0.95), respectively, with no difference in serious adverse events, including infection. The median monthly dose of ESA was 29,757 IU (IQR, 18,673–48,833) versus 38,805 IU (IQR, 24,377–60,620), with a median difference of −7539 IU per month (95% CI, −9485 to −5582). It is speculated that the dose-sparing effect of IV iron therapy on ESAs might contribute to the cardiovascular safety profile of high-dose IV iron. A proactive high-dose IV iron strategy is presumably cost effective given not only its improved clinical outcomes but also, decreased ESA utilization, which is less costly than IV iron in most health systems.

What Should Clinicians Do?

This landmark trial provides convincing evidence that a proactive high-dose IV iron strategy is not only safe but reduces ESA dosing and that it is also protective from a cardiovascular perspective. However, whether this can be generalized to all patients on HD is uncertain, because the PIVOTAL trial included only incident patients on HD for <12 months; individuals with infections (including viral hepatitis), malignancy, advanced heart failure, or limited life expectancies (*i.e.*, elderly, frail, or multi comorbidity) were excluded. Its effect on the United States HD population is also limited given that the mean ferritin and TSAT levels in the United States centers participating in the Dialysis Outcomes and Practice Patterns Study in February 2018 (10) were 827.74 ng/ml and 30.08% (both above the PIVOTAL trial's eligibility criteria and ferritin safety cutoff), suggesting that a liberal IV iron strategy has already been adopted in the United States. Whether additional increases in IV iron dosing and ferritin/TSAT targets above those used in the PIVOTAL trial (such as those used in the DRIVE study) are safe and effective is also uncertain. There is no compelling reason to believe that other IV iron formulations or administration schedules would alter the treatment effects seen in the PIVOTAL trial. The role of oral iron-based phosphate binders as an alternative or adjunct to IV iron needs additional investigation. Lastly, whether iron strategies will hold in the new era of hypoxia-inducible factors and recombinant fusion proteins remains to be determined.

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