Anemia Treatment After 30 Years of Erythropoietic Stimulating Agents: No Longer Business as Usual?

The publication date of this issue of ACKD, July-August 2019, is almost exactly 30 years after the approval by the Food and Drug Administration (FDA) of epoetin alfa in June 1989. There has been considerable evolution in the treatment of anemia in patients with CKD since that time despite the fact that erythropoietic stimulating agents (ESAs) remain the mainstay of that therapy. In the 1990s, we discovered the necessity of adequate iron supplementation to achieve the targeted erythropoietic response to ESAs. In the 2000s, we discovered that normalization of hemoglobin (Hb) levels in patients with CKD is associated with major adverse cardiovascular events (MACEs) compared to Hb targets in the 9-11.5 g/dL range. In the 2010s, we have seen increased choice of ESAs including longer acting agents and biosimilar forms; newer options for administration of iron including more bioavailable oral agents, a dialysate formulation, and evidence supporting the efficacy and safety of more proactive intravenous (IV) administration in hemodialysis (HD) patients; and an increased understanding of the role of hepcidin in the phenomenon called "ESA resistance." However, all of these advances have been refinements to an ESA-centric anemia treatment model in CKD without much in the way of disruptive technology. The hypoxia-inducible factor (HIF) stabilizers are that disruptive technology which, as of 2019, puts us at the threshold (or possibly precipice) of the first true revolution in anemia management in 3 decades.

WHERE WE ARE

In the wake of randomized controlled trials comparing Hb targets in the 9-11.5 g/dL to those in the 13-15 g/dL range, there remains considerable controversy regarding benefit vs risk of ESA therapy; practice guidelines, product labels, and payment policy leave us with a one-size-fits-all approach to anemia management. Patient preferences have been eliminated from this treatment model despite the fact that fatigue (which may or may not be anemia related) is one of the most common symptoms reported by patients with CKD.[1] Many patients may accept the risk of higher MACE at a target Hb level greater than that allowed by ESA dosing algorithms, FDA label guidance, and payment policy if the patients were given adequate information to make that choice. The Kidney Disease: Improving Global Outcomes guidelines acknowledge the importance of informed patient-centered decision making in this respect with a ceiling target Hb of 13 g/dL for those patients whose lifestyles would benefit from a higher Hb level and are willing to accept the MACE risk.[2] Since Hb > 12 g/dL is no longer a metric in either the US ESRD Quality Incentive Program or Dialysis Facility Compare, payment and public reporting policy should not be a disincentive to this component of patient-centered care.

It is clear that intermittent large doses of IV iron are an unphysiologic approach to iron replacement in anemic patients with iron deficiency. In non-dialysis dependent CKD (NDD-CKD) and peritoneal dialysis patients, traditional oral iron supplements have had variable success in repleting iron stores; ferric citrate[3] and those in the development pipeline (ferric maltol and sucrosomial/liposomal forms of oral iron) offer the promise of better bioavailability. Nonetheless, even these newer agents are not universally effective, and IV iron administration may be required. The latest generation of IV iron supplements such as ferumoxytol, ferric carboxymaltose, and iron isomaltoside (not yet approved in the United States) offer the advantages to NDD-CKD patients of larger doses per session which may decrease visits to the infusion center and venipunctures to precious venous real estate for future vascular access. For HD patients, IV iron is required in about 80% due to ongoing iron losses averaging 2-3 g/y.[4] The most physiologic way to replace these iron losses would be with small doses of iron administered frequently since only 3-4 mg iron is in the circulation bound to transferrin at any given time. Nonetheless, the most common protocols for administration of IV iron in HD units are in doses exceeding 50 mg per session because that is how the iron is packaged and less frequent doses of more iron require less nursing time. There are data suggesting that newer forms of iron administered in smaller doses more frequently decrease IV iron requirements in HD patients, thereby potentially decreasing the long-term toxicity of IV iron which may include tissue iron accumulation, oxidative stress to vascular endothelium, and infection risk. These newer forms of iron include oral ferric citrate[3] and ferric pyrophosphate citrate administered via the dialysate.[5] With or without such supplements, IV iron remains a mainstay of anemia treatment in HD patients. The controversy regarding the benefit vs risk of more aggressive IV iron replacement protocols has been addressed by the recently published Proactive IV Iron Therapy in Hemodialysis Patients (PIVOTAL) study which demonstrated that a proactive IV iron replacement protocol with a serum ferritin ceiling of 700 ng/mL was more effective (19% reduction in ESA dose at similar target Hb level) and safer (lower MACE) than a reactive IV iron replacement protocol with a ferritin floor of 200 ng/dL.[6] This offers some comfort to practitioners in the United States who have been prescribing sufficient IV iron to HD patients such that the mean serum ferritin is >800 ng/mL[7] despite Kidney Disease: Improving Global Outcomes

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recommendations that IV iron not be administered if the serum ferritin is >500 ng/mL.[2] How the results of the PIVOTAL study will affect future clinical practice remains to be seen.

The development of longer acting ESAs including darbepoetin alfa and methoxy polyethylene glycol-epoetin beta (CERA) would appear to be of more relevance to NDD-CKD and peritoneal dialysis patients who must receive their ESA subcutaneously and may need to visit a healthcare facility for the injection. Nonetheless, these longer acting agents have found significant market penetration in the HD patient population, driven by favorable contracting terms between the supplier and dialysis organizations and less nursing time required for administration. As of April 2018, according to the Dialysis Outcomes and Practice Patterns Study (DOPPS), epoetin alfa had 37.2%, darbepoetin alfa had 24.3%, and CERA had 38.5% market share among US HD patients.[8] Of some concern is a recent publication which retrospectively examined Japanese dialysis patients receiving ESAs.[9] It compared mortality risk between patients receiving short-acting ESAs (epoetin including a biosimilar form) and long-acting ESAs (darbepoetin and CERA). The authors used sophisticated statistical modeling to minimize the chance of residual confounding. Irrespective of the adjustment model, patients receiving long-acting ESAs had a higher rate of death from all causes, cardiovascular disease, cardiac disease, stroke, non-cardiovascular disease, stroke, and malignancy. The statistically significant hazard ratio persisted for all patient sub-groups except those with the lowest ESA dose and lowest erythropoietin resistance index, suggesting that the toxicity of long-acting ESAs is dose related. It should be noted that a previous study by Winkelmayer and colleagues[10] comparing long-term outcomes among US dialysis facilities using primarily darbepoetin vs epoetin found no differences between the groups. Only a long-term randomized controlled trial comparing short-acting vs long-acting ESAs can conclusively prove a cause and effect relationship between ESA duration of action and mortality risk. MIRCERA PASS (post-approval safety study) is an 8-year non-inferiority trial (median follow-up 3.4 years), yet to be published, comparing CERA with short-acting ESAs. The results were presented at ASN 2018 Kidney Week and revealed no difference between the two groups in MACE or all-cause mortality.[11]

WHERE WE'RE GOING

The discovery of hepcidin has been a breakthrough in our understanding of the control of iron absorption and internal disposition. This control system likely evolved as a defense mechanism against siderophilic pathogens; the inflammatory response which stimulates hepcidin leads to a reduction in blood iron levels through decreased absorption of iron from the gastrointestinal tract and decreased release of iron from macrophages where it is stored. This "anemia of chronic disease" is particularly common in CKD, an inflammatory state, and results in iron restricted erythropoiesis with or without ESA therapy. Both high ESA doses and high iron doses may be required to overcome the decreased delivery of iron to the erythroid marrow in the presence of high hepcidin levels, leading to potential toxicity from both these therapies. A variety of agents are in the development pipeline targeting the action of hepcidin in anemic patients with CKD. These include monoclonal antibodies directed against hepcidin itself, agents directed against pro-inflammatory cytokines that stimulate hepcidin production such as interleukin-6 and transforming growth factor-α, and agents directed against intermediaries in the hepcidin signaling pathway.

HIF stabilizers belong to a new class of orally administered drugs to treat anemia in patients with CKD.[12] HIF is present in nearly all tissues and constitutes the body's natural mechanism to adapt to hypoxic conditions. HIF is a heterodimer consisting of an alpha and beta subunit. The alpha subunit is rapidly degraded by a proline hydroxylase (PH) enzyme in the presence of oxygen, thereby preventing the heterodimerization with the beta subunit and its transcriptional effects on over 4000 genes, depending on the tissue. Activation of these genes leads to increased red blood cell production through increased synthesis of erythropoietin and the erythropoietin receptor as well as increased synthesis of a variety of iron handling proteins including transferrin, transferrin receptor, duodenal cytochrome B, divalent metal transporter-1, and ceruloplasmin. The net effect is a more "complete" stimulation of erythropoiesis than can be achieved by ESAs alone which do not affect iron metabolism. However, HIF stabilizers also stimulate a variety of genes not affecting erythropoiesis including those which affect angiogenesis, glucose metabolism, extracellular matrix production, and cellular proliferation. The HIF stabilizers under development have attempted to achieve specificity for erythropoiesis by targeting specific PH enzymes and with pharmacokinetics that allow for periods between doses during which there is no PH inhibition so that the effect of these agents on non-targeted genes can be minimized. There are 3 HIF stabilizers currently under development in the United States: roxadustat, vadadustat, and daprodustat. Roxadustat has a half-life of 12-13 hours and has been shown to be effective in raising Hb levels when administered 3 times weekly; vadadustat and daprodustat have half-lives of around 4 hours and are administered daily. Multiple phase 2 studies have been published with all 3 agents demonstrating comparable efficacy in maintaining Hb levels within target range when dialysis patients are switched from ESAs and in raising Hb levels to target range in ESA-naïve dialysis and NDD-CKD patients. Because of their beneficial effects on iron metabolism which lead to an increase in oral iron absorption, increased release of stored iron from macrophages, and increased transport of iron to the erythroid marrow, HIF stabilizers have been shown to be equally effective with oral or IV iron in the short term,[13] although it unlikely this can be sustained over the long term in HD patients given their ongoing iron losses. The use of HIF stabilizers has been shown to decrease hepcidin levels, although this is thought to be mediated by increased erythroferrone released by RBC precursors in the setting of accelerated erythropoiesis, not a direct effect of the

HIF stabilizers. Nonetheless, HIF stabilizer therapy has demonstrated comparable responsiveness in raising Hb levels among patients with normal or high CRP levels, the latter being a surrogate for the inflammatory conditions that typically lead to "ESA resistance."[14] Chinese phase 3 studies of roxadustat presented at 2018 ASN Kidney Week[14,15] demonstrated efficacy non-inferiority to ESA in end-stage kidney disease (ESKD) patients and superiority to placebo in NDD-CKD patients. However, these studies were not adequately powered for MACE outcomes (<1000 patients, 6 months of duration). Roxadustat has been approved for use in China by Chinese regulatory authorities.

Prior to the release of long-term (3 year) safety data, it is difficult to predict what the role of HIF stabilizers will be in the treatment of anemia in patients with CKD. Even with 3-year MACE data, there may still be reservations regarding the widespread adoption of these agents because it may take more than 3 years to determine their non-MACE effects such as angiogenesis (tumor growth, diabetic retinopathy), altered glucose metabolism, rate of renal function decline in NDD-CKD patients, and pulmonary hypertension. The appeal of an oral anemia therapy in non-HD patients is undeniable, even without longer term safety data. A reasonable approach in the non-HD population would be to discuss the risks and benefits of ESAs vs HIF stabilizers so the patient can make an informed decision balancing convenience with possible unknown risk. The same risk vs benefit discussion applies to the HD population where the motivation to abandon the parenterally administered ESA class of drugs with 30 years clinical experience is less compelling except if the patient is ESA resistant.

HOW WILL THIS BE PAID FOR?

No discussion of pharmacotherapy should occur without consideration of cost and payment. The cost of treating anemia in patients with CKD is highly visible to payers and is the major driving force in Medicare's moving from a fee-for-service to a prospective payment system (PPS or "bundling") for ESKD patients in 2011. Despite more conservative ESA use following the implementation of the PPS, it is estimated from cost reports that ESAs for ESKD patients in the United States exceeded $1.7 billion in 2016.[16] Payment for ESAs in NDD-CKD patients is determined by the patient's prescription drug plan, many of which have high co-pays that may be a barrier to ESA use. Almost all pharmacy benefit managers require prior authorization for ESAs, and many are now requiring that the patient receive epoetin alfa-epbx, the biosimilar epoetin alfa approved in the United States which is their least expensive ESA, unless there is a compelling reason why the patient should receive a brand name ESA. The pricing of HIF stabilizers has yet to be determined, so a value proposition cannot be quantified. Because HIF stabilizers will be approved by the FDA during or after 2020, their use in ESKD patients will quality for the "transitional drug add-on payment adjustment (TDAPA)" to the ESKD PPS.[17] Each HIF stabilizer will be paid for by the Centers for Medicare and Medicaid Services outside the dialysis payment "bundle" for 2 years following its approval by the FDA. In other words, for those 2 years the HIF stabilizer will be paid for through Medicare part D or Medicaid and will not cost the dialysis provider anything. The bundled payment for patients using an HIF stabilizer through TDAPA will be reduced by the average cost of ESA per treatment, which is around $30. Thus, if a patient's ESA dose costs more than an average of $30 per treatment, the dialysis facility will save money if an HIF stabilizer is used rather than an ESA. This provides a perverse economic, non-clinical, non-patient-centered incentive to use HIF stabilizers which it is hoped will be resisted. After its 2-year TDAPA period, each HIF stabilizer will not go into the dialysis payment bundle, but will rather be charged to Centers for Medicare and Medicaid Services by the dialysis provider as an "outlier payment" which is not fully reimbursed. At that point there may again be a perverse economic incentive to return to ESAs which remain in the bundle, or there may be competition which brings the price of all anemia treatments down.

Ultimately, the treatment of anemia in patients with CKD is a microcosm of Berwick's triple aim[18]: (1) population-driven, evidence-based, one-size-fits-all medicine with performance metrics; (2) patient-centered decision making and satisfaction with individual outcomes; and (3) the quest for payment policies which align incentives. The dawn of innovative anemia treatments gives stakeholders (physicians, health systems, dialysis organizations, payers, and patients) a rare opportunity to reassess the balance of this dynamic interplay and to chart a course that, while being evidence-based, encourages patients to assume a greater role in therapeutic decision making as new product choices become available, less constrained by unyielding clinical performance metrics, and within the guardrails of fiscal responsibility that recognizes the total, long-term cost of care and not just the price tag of today's medications.

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