targets of antifibrotic therapy. Although the clinical utility of antagomirs in CKD still needs to be demonstrated, the pivotal role of miRNAs in renal medicine opens a fascinating perspective. A growing list of randomized controlled trials aimed at halting renal disease progression with the available drugs resulted in rather counterintuitive and unexpected negative results;[23] thus, the great hope to treat kidney diseases relies on studies unlocking the genome that pave the way to discover better targeted therapeutic tools.

DISCLOSURES

None.

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See related article, "miR-150 Promotes Renal Fibrosis in Lupus Nephritis by Downregulating SOCS1," on pages 1073–1087.

Is Iron Maintenance Therapy Better Than Load and Hold?

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The history of intravenous (IV) iron for anemia management in patients undergoing maintenance dialysis makes

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for a most fascinating, educational, and clinically relevant story. 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 CKD: (*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 patients with CKD independent of the background cause of anemia, be it erythropoietin or iron deficiency, inflammation-related hyperhepcidinemia, or other hematologic and nonhematologic conditions? (*3*) What is the best iron agent and what is the optimal strategy for iron therapy in patients with non–dialysis-dependent CKD versus patients receiving long-term dialysis in terms of dose, frequency, and route (oral versus parenteral), and do outcomes differ 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 when needed)? (*4*) Does the type of vascular access (catheter versus arteriovenous shunt) or dialysis therapy modality (including peritoneal versus hemodialysis and conventional versus frequent hemodialysis) affect iron store status and the amount of iron loss, and, hence, is the 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? Finally, (*6*) what are the most reliable tests with which to assess iron status in patients with CKD, including conventional (serum iron, ferritin, and transferrin saturation ratio) versus more novel (content of reticulocyte hemoglobin, zinc protoporphyrin, percentage of hypochromic erythrocytes, hepcidin) iron markers versus elaborate tests (liver scanning 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 more than a quarter of a century of CKD anemia management, we still lack clear consensus on whether increasing hemoglobin levels with ESAs is safe[1] and on whether ESAs improve patient-centered outcomes, even though 10%–25% of the dialysis 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 anyone 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 patients with CKD and cancer, including exceptionally rigorous APPRISE (Assisting Providers and cancer Patients with Risk information for the Safe use of ESAs) 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 patients undergoing long-term dialysis are not frequently questioned, and although maintenance dosing of ESAs—usually 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 more than 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 among patients who received placebo.[3] Although this historical study had many 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 at any sign of or concern for infection.[2] (*2*) In the pre-ESA era, several 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 similar ferritin levels ranging from 5000 to 20,000 ng/ml, implicating IV iron administration are almost nonexistent. (*3*) Several *in vitro* studies have indicated 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 suggested 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 using 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. In addition, no studies have shown that liver iron in dialysis patients correlates with morbidity or mortality.

Assuming that there may still be reasons 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 increase in IV iron therapy for managing long-term 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 *JASN,* Brookhart *et al.*[13] examine a contemporary (2004–2008) cohort of approximately 120,000 hemodialysis patients from all DaVita dialysis units across the United States who received 776,203 unique IV iron administrations. They sought to systematically evaluate the association

between iron therapy dosing and frequency over 1-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 per month) versus high (>200 mg per month) IV iron dose, as well as "repletion" ("load-and-hold") iron therapy (*i.e.*, boluses of a large amount of IV iron, such as 300–1000 mg divided by 3–10 doses over several consecutive hemodialysis treatment sessions, usually over a short period of 1–3 weeks) versus "maintenance" iron therapy (*i.e.*, weekly, biweekly, or monthly administration of small amounts of IV iron, such as 25–100 mg at each administration) to maintain consistent iron administration without any interruption. During the exposure period, more than one third of patients did not receive IV iron, whereas 49% and 12% received maintenance and bolus therapies, respectively. Compared with the maintenance group, patients receiving bolus therapy had 25 additional infection-related hospitalizations per 1000 patient-years during the 3-month follow-up period, whereas maintenance iron therapy was not associated with worse outcomes compared with nontreatment.[13] Bolus iron therapy was also associated with an 11% higher death risk due to infectious diseases compared with maintenance therapy.

Whereas this rigorous study by Brookhart *et al.*[13] suggests that maintenance iron supplementation in hemodialysis patients is safe and is associated with fewer infection-related hospitalizations and deaths than "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 nonrandomized design may be fraught by confounding by medical indication, which is often not amenable to multivariate adjustment, even if novel and sophisticated methods are used.[14] That the risk of bolus iron therapy was highest 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, 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; they may call for re-examination of the current guidelines on iron therapy with regard to the amount, frequency, and interval of IV iron infused and whether more accurate and noninvasive methods for monitoring iron stores should be explored.

Notwithstanding the fact that IV iron therapy may lead to allergic reactions, oxidative stress, promotion of bacterial growth, and impairment of host defenses, the decades-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 comorbid conditions of uremic patients is probably 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, despite sporadic reports of a possible association 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. On the contrary, these studies 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 proinflammatory cytokine TNF-α can be reduced by IV iron therapy in patients with CKD.[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–100 mg per dose, to any infection-free hemodialysis patient who receives maintenance ESA therapy and whose serum ferritin is <1200 ng/ml.

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DISCLOSURES

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See related article, "Infection Risk with Bolus versus Maintenance Iron Supplementation in Hemodialysis Patients," on pages 1151–1158.

Ideal Cardiovascular Health and Progression of CKD: Perhaps not so "Simple"

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CKD is a global public health challenge. More than 13 million adults in the United States have moderate to severe CKD.[1] The prevalence of CKD has increased over time, in part due to the higher prevalence of diabetes and hypertension and the aging population.[2,3] Importantly, elderly adults with CKD are 13-fold more likely to die than reach advanced CKD requiring renal replacement therapy (CKD 5D), with cardiovascular disease being the leading cause of death.[4] Identifying health behaviors and health factors that lower the risk of progressive kidney dysfunction and death in the CKD population is paramount to optimizing health and longevity. In 2010, the American Heart Association (AHA) published "Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction: The American Heart Association's Strategic Impact Goal Through 2020 and Beyond," wherein the concept of ideal cardiovascular health was defined.[5] Ideal cardiovascular health is a conceptual framework that includes favorable health behaviors and health factors such as abstinence from smoking, an ideal body mass index (BMI), routine physical activity, a healthy diet, an untreated cholesterol $<$200 mg/dl, an untreated BP $<$120/80 mmHg, and the absence of diabetes mellitus. Although these health behaviors and factors define ideal cardiovascular health, these metrics correlate with general health, longevity, and prevention of other chronic diseases including CKD.[5] The AHA has developed Life's Simple 7 and the My Life Check,[6] which focus on optimizing these key modifiable health behaviors and factors.

In this issue of *JASN*, Muntner *et al.*[7] examined the association between the AHA's Life's Simple 7 and the incidence of CKD 5D in Reasons for Geographic and Racial Differences in Stroke (REGARDS) study participants with an estimated GFR (eGFR) $<$60 ml/min per 1.73 m^2. All-cause death was examined in secondary analyses. REGARDS participants' BP, total cholesterol, serum glucose, cigarette smoking, physical activity, diet, and BMI were each classified as poor, intermediate, or

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