

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.

REFERENCES

- Bhatt K, Mi QS, Dong Z: microRNAs in kidneys: Biogenesis, regulation, and pathophysiological roles. *Am J Physiol Renal Physiol* 300: F602–F610, 2011
- Nagalakshmi VK, Ren Q, Pugh MM, Valerius MT, McMahon AP, Yu J: Dicer regulates the development of nephrogenic and ureteric compartments in the mammalian kidney. *Kidney Int* 79: 317–330, 2011
- Sun Y, Koo S, White N, Peralta E, Esau C, Dean NM, Perera RJ: Development of a micro-array to detect human and mouse microRNAs and characterization of expression in human organs. *Nucleic Acids Res* 32: e188, 2004
- Chandrasekaran K, Karolina DS, Sepramaniam S, Armugam A, Wintour EM, Bertram JF, Jeyaseelan K: Role of microRNAs in kidney homeostasis and disease. *Kidney Int* 81: 617–627, 2012
- Gebeshuber CA, Kornauth C, Dong L, Sierig R, Seibler J, Reiss M, Tauber S, Bilban M, Wang S, Kain R, Böhmig GA, Moeller MJ, Gröne HJ, Englert C, Martinez J, Kerjaschki D: Focal segmental glomerulosclerosis is induced by microRNA-193a and its downregulation of WT1. *Nat Med* 19: 481–487, 2013
- Chung AC, Dong Y, Yang W, Zhong X, Li R, Lan HY: Smad7 suppresses renal fibrosis via altering expression of TGF- β /Smad3-regulated microRNAs. *Mol Ther* 21: 388–398, 2013
- Qin W, Chung AC, Huang XR, Meng XM, Hui DS, Yu CM, Sung JJ, Lan HY: TGF- β /Smad3 signaling promotes renal fibrosis by inhibiting miR-29. *J Am Soc Nephrol* 22: 1462–1474, 2011
- Lan HY, Chung AC: TGF- β /Smad signaling in kidney disease. *Semin Nephrol* 32: 236–243, 2012
- Liang D, Shen N: MicroRNA involvement in lupus: The beginning of a new tale. *Curr Opin Rheumatol* 24: 489–498, 2012
- Lu MC, Lai NS, Chen HC, Yu HC, Huang KY, Tung CH, Huang HB, Yu CL: Decreased microRNA(miR)-145 and increased miR-224 expression in T cells from patients with systemic lupus erythematosus involved in lupus immunopathogenesis. *Clin Exp Immunol* 171: 91–99, 2013
- Carlsen AL, Schetter AJ, Nielsen CT, Lood C, Knudsen S, Voss A, Harris CC, Hellmark T, Segelmark M, Jacobsen S, Bengtsson AA, Heegaard NH: Circulating microRNA expression profiles associated with systemic lupus erythematosus. *Arthritis Rheum* 65: 1324–1334, 2013
- Dai Y, Sui W, Lan H, Yan Q, Huang H, Huang Y: Comprehensive analysis of microRNA expression patterns in renal biopsies of lupus nephritis patients. *Rheumatol Int* 29: 749–754, 2009
- Lu J, Kwan BC, Lai FM, Tam LS, Li EK, Chow KM, Wang G, Li PK, Szeto CC: Glomerular and tubulointerstitial miR-638, miR-198 and miR-146a expression in lupus nephritis. *Nephrology (Carlton)* 17: 346–351, 2012
- Zhou H, Hasni SA, Perez P, Tandon M, Jang S, Zheng C, Kopp JB, Austin H 3rd, Balow JE, Alevizos I, Illei GG: miR-150 promotes renal fibrosis in lupus nephritis by downregulating SOCS1. *J Am Soc Nephrol* 24: 1073–1087, 2013
- Macconi D, Tomasoni S, Romagnani P, Trionfini P, Sangalli F, Mazzeo B, Rizzo P, Lazzeri E, Abbate M, Remuzzi G, Benigni A: MicroRNA-324-3p promotes renal fibrosis and is a target of ACE inhibition. *J Am Soc Nephrol* 23: 1496–1505, 2012
- Ronconi E, Sagrinati C, Angelotti ML, Lazzeri E, Mazzeo B, Ballerini L, Parente E, Becherucci F, Gacci M, Carini M, Maggi E, Serio M, Vannelli GB, Lasagni L, Romagnani S, Romagnani P: Regeneration of glomerular podocytes by human renal progenitors. *J Am Soc Nephrol* 20: 322–332, 2009
- Benigni A, Morigi M, Rizzo P, Gagliardini E, Rota C, Abbate M, Ghezzi S, Remuzzi A, Remuzzi G: Inhibiting angiotensin-converting enzyme promotes renal repair by limiting progenitor cell proliferation and restoring the glomerular architecture. *Am J Pathol* 179: 628–638, 2011
- Fujimoto M, Tsutsui H, Xinshou O, Tokumoto M, Watanabe D, Shima Y, Yoshimoto T, Hirakata H, Kawase I, Nakanishi K, Kishimoto T, Naka T: Inadequate induction of suppressor of cytokine signaling-1 causes systemic autoimmune diseases. *Int Immunol* 16: 303–314, 2004
- Ortiz-Muñoz G, Lopez-Parra V, Lopez-Franco O, Fernandez-Vizarrá P, Mallavia B, Flores C, Sanz A, Blanco J, Mezzano S, Ortiz A, Egido J, Gomez-Guerrero C: Suppressors of cytokine signaling abrogate diabetic nephropathy. *J Am Soc Nephrol* 21: 763–772, 2010
- Chan HC, Ke LY, Chang LL, Liu CC, Hung YH, Lin CH, Li RN, Tsai WC, Liu HW, Yen JH: Suppressor of cytokine signaling 1 gene expression and polymorphisms in systemic lupus erythematosus. *Lupus* 19: 696–702, 2010
- Krishnan MR, Wang C, Marion TN: Anti-DNA autoantibodies initiate experimental lupus nephritis by binding directly to the glomerular basement membrane in mice. *Kidney Int* 82: 184–192, 2012
- Metcalf JL, Bradshaw PS, Komosa M, Greer SN, Stephen Meyn M, Ohh M: K63-Ubiquitylation of VHL by SOCS1 mediates DNA double-strand break repair [published online ahead of print March 4, 2013]. *Oncogene* doi:10.1038/onc.2013.22
- Thomas MC: Emerging drugs for managing kidney disease in patients with diabetes. *Expert Opin Emerg Drugs* 18: 55–70, 2013

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?

Connie M. Rhee*[†] and Kamyar Kalantar-Zadeh*^{†‡}

*Harold Simmons Center for Kidney Disease Research & Epidemiology, Orange, California; [†]University of California Irvine Medical Center, Orange, California; and [‡]Department of Epidemiology, University of California Los Angeles School of Public Health, Los Angeles, California

J Am Soc Nephrol 24: 1028–1031, 2013.
doi: 10.1681/ASN.2013050456

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

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Kamyar Kalantar-Zadeh, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine School of Medicine, 101 The City Drive South, City Tower, Orange, CA 92868-3217. Email: kkz@uci.edu

Copyright © 2013 by the American Society of Nephrology

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 safe¹ 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 disease⁷ or death risk⁸ 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* studies⁵ 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.

ACKNOWLEDGMENTS

C.M.R. is supported by a National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) grant (F32 DK093201). K.K.Z. is supported by research grants from the NIH/NIDDK (R01-DK078106, K24-DK091419) and a philanthropic grant from Mr. Harold Simmons.

DISCLOSURES

Dr. Kalantar has served as a consultant to Amgen, DaVita, Fresenius, Keryx, and Vifor.

REFERENCES

- Kalantar-Zadeh K, Streja E, Miller JE, Nissenson AR: Intravenous iron versus erythropoiesis-stimulating agents: Friends or foes in treating chronic kidney disease anemia? *Adv Chronic Kidney Dis* 16: 143–151, 2009
- Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH: The fascinating but deceptive ferritin: To measure it or not to measure it in chronic kidney disease? *Clin J Am Soc Nephrol* 1[Suppl 1]: S9–S18, 2006
- Murray MJ, Murray AB, Murray MB, Murray CJ: The adverse effect of iron repletion on the course of certain infections. *BMJ* 2: 1113–1115, 1978
- Waterlot Y, Cantinieaux B, Hariga-Muller C, De Maertelaere-Laurent E, Vanherweghem JL, Fondou P: Impaired phagocytic activity of neutrophils in patients receiving haemodialysis: The critical role of iron overload. *Br Med J (Clin Res Ed)* 291: 501–504, 1985
- Zager RA, Johnson AC, Hanson SY, Wasse H: Parenteral iron formulations: A comparative toxicologic analysis and mechanisms of cell injury. *Am J Kidney Dis* 40: 90–103, 2002
- Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH: Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. *Am J Kidney Dis* 37: 564–572, 2001
- Drüeke T, Witko-Sarsat V, Massy Z, Descamps-Latscha B, Guerin AP, Marchais SJ, Gausson V, London GM: Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. *Circulation* 106: 2212–2217, 2002
- Feldman HI, Santanna J, Guo W, Furst H, Franklin E, Joffe M, Marcus S, Faich G: Iron administration and clinical outcomes in hemodialysis patients. *J Am Soc Nephrol* 13: 734–744, 2002
- Feldman HI, Joffe M, Robinson B, Knauss J, Cizman B, Guo W, Franklin-Becker E, Faich G: Administration of parenteral iron and mortality among hemodialysis patients. *J Am Soc Nephrol* 15: 1623–1632, 2004
- Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, Roy M, Machado G, Jankiewicz P, Drahi G, Dahan H, Cohen Y: Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: An MRI study. *Am J Med*. 2012;125:991–999
- Keung YK, Owen J: Iron deficiency and thrombosis: Literature review. *Clin Appl Thromb Hemost* 2004;10:387–391
- Streja E, Kovesdy CP, Greenland S, Kopple JD, McAllister CJ, Nissenson AR, Kalantar-Zadeh K: Erythropoietin, iron depletion, and relative thrombocytosis: A possible explanation for hemoglobin-survival paradox in hemodialysis. *Am J Kidney Dis* 52: 727–736, 2008
- Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV: A comparison of intravenous iron supplementation strategies and infection risk in hemodialysis patients. *J Am Soc Nephrol*. 24: 1151–1158, 2013
- Kovesdy CP, Kalantar-Zadeh K: Observational studies versus randomized controlled trials: Avenues to causal inference in nephrology. *Adv Chronic Kidney Dis* 19: 11–18, 2012
- Salonen JT, Nyyssönen K, Korpela H, Tuomilehto J, Seppänen R, Salonen R: High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 86: 803–811, 1992
- Sempos CT, Looker AC, Gillum RF, Makuc DM: Body iron stores and the risk of coronary heart disease. *N Engl J Med* 330: 1119–1124, 1994
- Kalantar-Zadeh K, McAllister CJ, Lehn RS, Liu E, Kopple JD: A low serum iron level is a predictor of poor outcome in hemodialysis patients. *Am J Kidney Dis* 43: 671–684, 2004
- Weiss G, Meusbürger E, Radacher G, Garimorth K, Neyer U, Mayer G: Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. *Kidney Int* 64: 572–578, 2003

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”

Andrew I. Chin and Lorien S. Dalrymple

Division of Nephrology, Department of Medicine, University of California, Davis, California

J Am Soc Nephrol 24: 1031–1033, 2013.
doi: 10.1681/ASN.2013040388

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 m². 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

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Lorien S. Dalrymple, Division of Nephrology, University of California, Davis, 4150 V Street, Suite 3500, Sacramento, CA 95817. Email: Lorien.Dalrymple@ucdmc.ucdavis.edu

Copyright © 2013 by the American Society of Nephrology