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Emerging Challenges of Anemia Management in CKD

Erythropoiesis and iron homeostasis are distorted in chronic kidney disease (CKD) as a result of a complex chain of events, including the relative deficiency of erythropoietin, chronic inflammation, blood loss, decreased iron absorption and utilization, and exogenous iron and erythropoietin acquisition via biologically unregulated mechanisms (blood transfusions and medicinal erythropoietin and iron administration). The 1970s and 1980s exemplify the era before the synthetic production of the erythropoiesis-stimulating agents (ESA), characterized by 1-digit hemoglobin levels in dialysis patients, frequent blood transfusion, and the occurrence of cases with massive iron overload. In the post-ESA era, we expect to experience more iron deficiency in CKD patients, although this expectation is somewhat confounded by increasing levels of blood hemoglobin and serum ferritin over the past 15 years.

Undoubtedly, the advent of ESA and various intravenous iron preparations has resulted in a much more effective management of anemia of CKD, allowing us to maintain hemoglobin levels in certain desired ranges and to effectively treat iron deficiency. Among the emerging challenges are the risks associated with administering high ESA and iron doses, leading to elevated hemoglobin levels and iron overload. Goal-oriented treatment strategies targeting “desirable” hemoglobin and iron levels are now the norm in clinical nephrology. The relative ease of achieving predefined hemoglobin and iron levels has led to the emergence of questions about what these ideal levels should be and how such levels could be best achieved.

The field of anemia management in CKD will continue to evolve, no doubt. We know now that “higher is better” is not necessarily true, although we still debate why. Novel ESA and iron components are emerging,

leading to questions about relative risks and benefits associated with certain agents versus others. And, finally, with the expected introduction of bundled payments in the dialysis arena in the United States, our outlook on how to manage anemia of CKD may undergo fundamental changes.

This issue of the *Advances in Chronic Kidney Disease* brings together some of the leading authorities in the field of CKD anemia to examine various, often controversial, aspects of the epidemiology, diagnosis, and therapy of ESA therapy and iron-related abnormalities in CKD. Adamson provides a description of various pathophysiologic mechanisms of ESA hyporesponsiveness in CKD. Yee reviews the definition of hemoglobin variability, its contributors, and associated adverse consequences and follows with a delineation of clinical causes of ESA hyporesponsiveness and its consequences. Agarwal describes the intricate interrelationships among iron metabolism, inflammation, and oxidative stress in CKD and chronic disease states. He also examines the various and often deceptive faces of ferritin. Wish introduces us to the more mundane but absolutely critical financial and regulatory aspects of CKD anemia management in the United States, with an eye toward the expected changes once bundling is implemented. Kovesdy examines the epidemiology of iron abnormalities in patients with non-dialysis-dependent CKD and parallels them with findings from studies in dialysis patients. Macdougall introduces us to novel ESAs and iron products and gives us a glimpse of the underground ESA market dominated by unregulated entities. Besarab revisits the issue of the “ideal” hemoglobin level, fresh with new data from randomized controlled trials and epidemiologic studies. Finally, Kalantar-Zadeh contrasts the 2 main ingredients of our anti-anemia armamentarium (iron and ESA) and argues that they should be friends not foes.

The confluence of academic, therapeutic, and commercial interests has made anemia management one of the hottest topics in

CKD in the last 2 decades. Continuing shifts within this field will ensure that there will be no cooling off of it in the near future.

In summary, this issue of the *Advances in Chronic Kidney Disease* provides a unique compilation of articles by several thought leaders

in the field. We are certain that these will prove to be valuable reading material for both novices and experts.

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Guest Editors