Safety Issues in Iron Treatment in CKD

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Summary: Intravenous iron products are essential for the treatment of anemia in end-stage renal disease patients maintained on hemodialysis. Although proper use of these compounds is necessary for the prevention of iron deficiency, their indiscriminate use could potentially cause insidious adverse consequences. Iron overload can intensify the chronic kidney disease–associated oxidative stress, inflammation, and cardiovascular disease; increase the risk of infections; worsen the severity of type 2 diabetes; and exacerbate neurologic and cognitive dysfunction. These and other adverse effects largely are mediated by iron-catalyzed generation of reactive oxygen species. Unlike conventional oral iron products, the newly released iron-containing phosphate binder ferric citrate has been shown to increase iron stores in end-stage renal disease patients. Therefore, iron indices should be monitored in patients receiving this product. Two published studies have shown a high prevalence of hepatic iron loading among hemodialysis patients treated with erythropoiesis-stimulating agents and intravenous iron compounds. Given the potential risks related to iron treatment in this vulnerable population, studies to better understand safety are needed.
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Observational studies consistently have found an association between the severity of anemia and adverse outcomes in patients with chronic kidney disease (CKD). These findings prompted several randomized clinical trials in currently dialysis-independent and dialysis-dependent patients with CKD to test the hypothesis that correction of anemia may improve cardiovascular outcomes.[1–3] However, data analysis in those trials showed that patients assigned to the normal or near-normal hemoglobin targets experienced higher adverse outcomes than patients assigned to the lower hemoglobin targets. In the same studies, the subgroup of patients whose hemoglobin level could be normalized did considerably better.[1,4] In addition, the minority of end-stage renal disease (ESRD) patients who naturally maintain normal hemoglobin levels without requiring erythropoiesis-stimulating agents (ESAs) do not experience increased mortality.[5] Despite high doses of ESA and intravenous (IV) iron products, only a minority of patients randomized to the normal (21% in Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR)) or near-normal hemoglobin (38% in Cardiovascular Reduction Early Anemia Treatment Epoetin β (CREATE)) groups achieved the target.[1–3] As a result of implementation of the bundling reimbursement system in the United States and the high cost of ESAs, the ESA dosing has decreased and IV iron has increased and ferritin levels have continued to increase. This trend could potentially be harmful because iron could[6] amplify oxidative stress and inflammation, which are constant features of CKD/ESRD.[7–10]

The potential role of high doses of ESA in the pathogenesis of cardiovascular disease (CVD), thromboembolic disorders, and other complications has been reviewed previously[11,12] and will not be addressed here. This article provides an overview of the potential safety concerns with use of iron preparations. At physiologic ranges, iron is protein-bound so that it is safely liganded and kept catalytically inactive. However, when improperly liganded, H_2O_2, which is generated by mitochondria and inflammatory cells, reacts with ferrous iron. This leads to conversion of Fe^{2+} to Fe^{3+} and generation of the hydroxyl radical $\cdot OH$, which is a highly reactive free radical. Superoxide, produced by mitochondria and mono-oxygenase enzymes, in turn, converts the ferric back to ferrous iron (Haber–Weiss reaction), which provides the fuel for continuous $\cdot OH$ production and perpetuation of oxidative stress. Because free or incompletely liganded iron is catalytically active and causes oxidative stress and tissue injury, absorption, transport, and storage of iron, its retrieval from storage sites and its uptake by cells are tightly regulated. On each occasion, iron is bound to proteins such as transferrin in the plasma and ferritin in hepatocytes and reticuloendothelial cells, hemoglobin in erythrocytes, and myoglobin in myocytes, preventing exposure to the redox active iron.

When administered intravenously the biologic safeguards for handling and regulating iron are partially bypassed. Numerous in vitro and in vivo studies have

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shown the ability of IV iron compounds to promote oxidative stress and cell injury/death in cultured renal proximal tubular epithelial cells and endothelial cells.[13,14] Studies in CKD rats have shown persistent oxidative stress in the aorta, myocardium, and other organs several weeks after IV iron administration.[9,15] IV iron products, evaluated in a relatively small number of patients with ESRD, have shown significant increases in biomarkers of oxidative stress including lipid, protein, and DNA oxidation products and inflammatory mediators.[16–18] In the presence of inflammation, the release of proteases and secretion of hydrogen ion by lysosomes results in dissociation of iron from the binding proteins, further enabling iron to catalyze formation of reactive oxygen species (ROS).

IRON AND THE CARDIOVASCULAR SYSTEM

There is emerging evidence supporting the role of iron overload in cardiovascular complications. A recent study comparing the effect of oral versus parental iron in the CKD population was terminated early because the group receiving IV iron experienced a 2.51-fold higher incidence of cardiovascular events ($P < .001$) and a two-fold higher incidence of hospitalization for heart failure in the IV compared with the oral iron-treated group.[19]

Studies conducted in animals and cultured cells have identified the mechanisms of adverse cardiovascular effects of excess iron. For example, in cultured human endothelial cells, exposure to IV iron products inhibited proliferation, induced apoptosis, and up-regulated monocyte adhesion.[13,20] Endothelial dysfunction and injury play a central part in the pathogenesis of atherosclerosis, thrombosis, and CVD. Oxidative stress induces endothelial dysfunction via ROS-mediated inactivation of nitric oxide, depletion of nitric oxide synthase co-factor (tetrahydrobiopterin), and accumulation of the nitric oxide synthase inhibitor asymmetric dimethylarginine. In fact, IV iron products significantly reduce acetylcholine-induced vasorelaxation in isolated artery rings.[13,21] Similar responses have been identified in normal human subjects.[20,22] Increased plasma asymmetric dimethylarginine levels potentially predict cardiovascular events in ESRD patients.[23,24]

Carotid artery media-intima thickness, a marker of atherosclerosis, may be associated with the annual cumulative dose of IV iron preparations in ESRD patients.[25,26] Also, the severity of atherosclerotic lesions has been shown to be greater in patients with carotid lesions who had received long-term IV iron preparations.[26] Rabbits fed a high-cholesterol diet accumulate iron in the atherosclerosis plaques,[27,28] and atherosclerotic lesions in apolipoprotein E–deficient mice contain significant amounts of iron.[28] Iron accumulation also is higher in abdominal aortic aneurysm walls compared with non–aortic aneurysm walls.[29] Interaction between iron and lipoproteins can lead to foam cell apoptosis and plaque instability, a process that can precipitate acute cardiovascular events.[30–32] Conversely, reducing iron availability by chelation therapy in animal models of carotid injury significantly inhibits intimal thickening and vascular smooth muscle cell proliferation.[33] These mechanisms by which iron may exacerbate atherosclerosis and contribute to the development of vascular calcification could be relevant for patients with CKD.[34]

CONTRIBUTION OF IRON OVERLOAD TO SYSTEMIC INFLAMMATION AND INFECTIONS

CKD results in simultaneous activation and deficiency of the immune system.[35] Activation of the immune system in this population is responsible for systemic inflammation, a driving force behind many CKD-associated complications including atherosclerosis, CVD, cachexia, anemia, and numerous other morbidities. The CKD-associated immune deficiency results in impaired response to vaccination, high incidence, increased severity, and poor outcome of infections.

The CKD/ESRD-induced systemic inflammation is caused by activation of the innate and adaptive immune responses and impairment of the anti-inflammatory regulatory factors, events that are mediated by the following: (1) accumulation of proinflammatory oxidized low-density lipoprotein coupled with the deficiency of high-density lipoprotein and its reduced anti-inflammatory capacity[36,37]; (2) disruption of the intestinal epithelial barrier structure and altered intestinal microbiome, which promote systemic inflammation by enabling influx of endotoxin and other noxious products in the systemic circulation[38]; (3) increased population and sustained activation of monocytes, which is marked by their increased basal expressions of integrins, Toll-like receptors 2 and 4, and spontaneous production of cytokine and reactive oxygen species[39,40]; (4) impaired inhibitory activity and a reduced population of regulatory T lymphocytes, which are essential for mitigating inflammation[41]; (5) spontaneous activation, degranulation, and increased basal production of ROS by circulating polymorphonuclear leukocytes (PMNs)[39]; (6) increased ROS production and chemokine expression by the cellular constituents of various tissues[10,41,42]; and (7) co-existing conditions such as autoimmune diseases and diabetes.

The main causes of CKD-associated immune deficiency include the following: (1) depletion of dendritic cells, which are the primary antigen-presenting cells[43]; (2) reduced $CD4^+$ helper T-lymphocyte/$CD8^+$ suppressor T-lymphocyte ratio and depletion of naive and central memory T lymphocytes[44]; (3) diffuse depletion of B lymphocytes, which contributes to impaired