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# IRON THERAPY IN CHRONIC KIDNEY DISEASE: CURRENT CONTROVERSIES

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## SUMMARY

Anaemia in chronic kidney disease (CKD) is a complex disease that requires an integrated approach to incorporate both diagnostic and therapeutic interventions and to address the different facets of its aetiology and pathophysiology. The advent of erythropoiesis stimulating agents (ESA) has revolutionised the therapy of anaemia of CKD, and has resulted in a significant decline in the need for blood transfusions in CKD patients. The routine application of ESA has also led to the need for concomitant iron supplementation. ESA and iron therapy now form the cornerstone of anaemia management in CKD. Intravenous iron administration is effective with acceptable safety, and may improve ESA responsiveness. However, less is known about the long-term safety of iron supplementation in CKD patients. Whereas maintenance (weekly to monthly) intravenous iron has been routinely used in maintenance dialysis patients, iron replacement in patients with non-dialysis-dependent CKD is less well studied, in spite of the much larger number of patients affected. This review discusses iron supplementation in CKD with an emphasis toward controversial issues that continue to pose dilemmas in clinical practice. Concerns related to both the optimal amount of iron supplementation and to the safety of various agents available in clinical practice are presented.

**KEY WORDS** Anaemia • Chronic kidney disease • Erythropoiesis-Stimulating agents • Haemoglobin

## BIODATA

**Csaba Kovesdy** is Chief of Nephrology at Salem Veterans Affairs Medical Center and Assistant Professor of clinical internal medicine at the University of Virginia School of Medicine in Charlottesville, Virginia. He has authored or coauthored articles in many peer-reviewed journals including the *Journal of the American Society of Nephrology*, *Clinical Journal of the American Society of Nephrology*, *Kidney International* and *American Journal of Kidney Diseases*. He is a member of the American Society of Nephrology and the International Society of Nephrology. He lectures on topics related to chronic kidney disease, hypertension, bone and mineral disorders and other areas in clinical nephrology. His main research activities are concerned with epidemiology and outcomes, anaemia, bone and mineral disorders and nutrition in non-dialysis-dependent chronic kidney disease (CKD).



**Kamyar Kalantar-Zadeh** is the Associate Professor of medicine, pediatrics and epidemiology at UCLA David Geffen Schools of Medicine and Public Health. He has received many awards including from National Institutes of Health and National Kidney Foundation, and is a member of the editorial board of several renal journals including *American Journal of Kidney Diseases*, *Clinical Journal of the American Society of Nephrology*, *American Journal of Nephrology*, *Advances in Chronic Kidney Disease*, *International Urology and Nephrology*, *Clinical Nephrology*, *Journal of Renal Nutrition*, etc. He has co-authored 150 research papers and lectures frequently on nontraditional cardiovascular risk factors in patients with CKD such as malnutrition, inflammation-cachexia syndrome, iron and anaemia and bone and mineral disorders.



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**INTRODUCTION**

Anaemia is a common complication of chronic kidney disease (CKD) and is associated with poor outcomes including higher death risk in both maintenance dialysis patients (Regidor *et al.* 2006), and in individuals with non-dialysis-dependent CKD stages 3 to 5 (Kovesdy *et al.* 2006). Since the introduction of the first erythropoiesis stimulating agent (ESA), anaemia management has become a core component of everyday nephrology practice. Whereas the application of ESA therapy has significantly decreased the need for blood transfusions in dialysis patients, it has also resulted in the widespread use of intravenous (IV) iron supplements.

The results of recent clinical trials examining the effects of ESA (Singh *et al.* 2006) have highlighted potential problems stemming from treatments approved for short-term indications (in the above referenced study, the correction of anaemia via high ESA doses) without proper assessment of their long-term safety. Similar concerns exist for IV iron preparations, which are all currently approved for the treatment of iron deficiency in various stages of CKD, but whose long-term safety continues to be debated. Optimal iron management involves the administration of enough iron to assure unhindered erythropoiesis (provided enough erythropoietin is also available), but avoids deleterious consequences that are either the result of too much iron (irrespective of the therapeutic agent), or, that are related to reactions that are specific to the particular agent used.

We review our current understanding about what an optimal iron level means and discuss currently available IV iron products, together with the various concerns related to potential adverse effects of therapeutic iron administration.

**THE ROLE OF IRON IN CKD ANAEMIA**

Haemoglobin synthesis is suboptimal without the presence of iron (Fishbane *et al.* 2004), thus successful haematopoiesis in CKD necessitates the presence of both ESA and iron (Kalantar-Zadeh *et al.* 2009b). CKD patients may lose iron as a result of gastrointestinal or other bleeding, frequent blood testing or blood losses related to haemodialysis, and ESA use has magnified the absolute or relative iron deficiency caused by such losses (Kalantar-Zadeh *et al.* 2009a). Together with ineffective gastrointestinal iron absorption, this loss of iron can amount to a negative iron balance of 1.5 to 3 grams per year (Sakiewicz & Paganini 1998). Effective erythropoiesis requires the replacement of, at least, a similar amount of iron.

**IRON STORES: DIAGNOSTIC DILEMMAS**

Optimising iron management starts with a reliable assessment of iron stores. Unfortunately, the methods that are routinely available to achieve this have significant disadvantages. Table 1 shows laboratory markers of iron status that can be employed

Diagnostic marker	Strengths	Limitations
Bone marrow iron content, measured from biopsy	Gold standard.	Invasive test, semi (but not fully) quantitative.
Liver iron content, measured from biopsy	Gold standard.	Invasive test, semi (but not fully) quantitative.
Liver iron stores via SQUID	Noninvasive and safe method.	Investigational; limited experience available.
Serum ferritin	Low ferritin levels are highly specific for detection of iron deficiency.	Moderately high ferritin levels could occur in the setting of non-iron-related conditions.
Transferrin saturation ratio (iron saturation ratio) <sup>a</sup>	Higher sensitivity than serum ferritin to detect iron deficiency.	The denominator (TIBC) can be low in malnutrition and/or inflammation.
Serum iron	Direct measurement of circulating iron.	Diurnal fluctuation; can be low in inflammation.
Reticulocyte haemoglobin content	Measures immediate incorporation of iron into reticulocytes.	Limited data, reference levels debatable.
Percentage of hypochromic red cells	Similar to reticulocyte haemoglobin content.	Cumbersome specimen shipment interferes with the results.
Soluble transferrin receptor	Correlates with the number of transferrin receptors on erythroblasts.	Mixed applicability data, unknown cut-off levels.
Erythrocyte zinc protoporphyrin	May be less confounded by inflammation.	Affected by non-iron-related factors such as lead level.
Hepcidin	May detect the presence of functional iron deficiency due to inflammation.	Currently there are no reliable assays for its measurement.

Table 1: Markers of iron stores in CKD patients (adapted from Kalantar-Zadeh *et al.* 2006).

<sup>a</sup>Calculated by dividing serum iron by total iron binding capacity (TIBC).

SQUID = Superconducting quantum interference device.

to assess an individual's iron stores. Commonly used iron markers are serum iron, the iron saturation ratio (ISAT, also known as the transferrin saturation ratio [TSAT]), and serum ferritin. The gold standard method for assessment of iron stores is the semiquantitative staining of bone marrow iron, but this is rarely used due to its invasive nature (Fishbane *et al.* 2001; Kaneko *et al.* 2003). Similarly, direct liver iron store assessment requires a liver biopsy, although an indirect assessment via the *Superconducting Quantum Interference Device* (SQUID) may become an option in the future (Asanuma *et al.* 2005). Other nontraditional but much less frequently utilised iron markers include the reticulocyte haemoglobin content (Fishbane *et al.* 2001; Kaneko *et al.* 2003), the percentage of hypochromic red cells (Asanuma *et al.* 2005), and levels of soluble transferrin receptor (Bovy *et al.* 1999), erythrocyte zinc protoporphyrin (Chiang *et al.* 2002) and hepcidin (Malyszko *et al.* 2005). With the exception of serum iron, TSAT and ferritin, none of these measures are currently routinely applied in the United States, even though the percentage of hypochromic red cells and the reticulocyte haemoglobin content are available if needed, (Wish 2006) and European guidelines recommend their routine use in clinical practice (European Renal Assoc.—European Dialysis and Transplant Assoc. 2004). Furthermore, most of these so-called measures of iron stores are susceptible to being confounded by inflammation or other non-iron-related factors (see Table 1), long-term studies of outcomes using these tests in CKD are missing and they also do not provide information on iron overload (Kalantar-Zadeh *et al.* 2005a). As a result, serum ferritin and TSAT remain the only routine tools available in clinical practice to assess the iron status in the United States.

A common problem in everyday practice is a discrepancy in the routinely applied measures of iron stores, most often when a low or normal TSAT is coupled with an elevated serum ferritin level. This group most often signals confounding conditions that affect serum ferritin level (Rambod *et al.* 2008). During the *acute phase response*, proinflammatory cytokines such as interleukin-1 beta (IL-1 $\beta$ ) and tumour necrosis factor alpha (TNF- $\alpha$ ) increase the synthesis of ferritin through an increased translation of preformed ferritin mRNA (Rogers *et al.* 1990; Kwak *et al.* 1995; Harrison and Arosio 1996). The reason for increased ferritin synthesis under inflammatory conditions is unclear. Hypothetically, higher amounts of ferritin may trap more body iron to protect from bacterial infection. This may result in so-called "functional iron deficiency," which may be

useful in acute inflammation, but harmful (and leading to refractory anaemia) in chronic disease states that are characterised by inflammation that is unrelated to bacterial infections. IL-1 $\beta$  induces ferritin gene expression by translational control of mRNA, but unlike the iron-dependent ferritin gene expression, it also requires the background presence of some cellular iron (Rogers *et al.* 1994). The permissive role of minimal iron in regulating inflammatory synthesis of ferritin is consistent with recent clinical and epidemiologic findings in CKD patients, in whom, under *absolute* iron deficiency, the serum ferritin is almost always low, even in the presence of inflammation. But once minimally required iron is available, ferritin regulation becomes a function of non-iron-dependent factors such as inflammation (Kalantar-Zadeh *et al.* 2004b). This may explain why most studies have found a superior *specificity* for a low serum ferritin in diagnosing iron deficiency, whereas its *sensitivity* is poor (Kalantar-Zadeh *et al.* 1995; Fishbane *et al.* 2004). Therefore, a low ferritin level appears to be a reliable indicator of iron deficiency, while a normal-to-moderately high serum ferritin (which is a common finding in dialysis patient, Figure 1) is a poor diagnostic test as it does not rule out iron deficiency, nor does it indicate adequate or elevated iron stores (Kalantar-Zadeh *et al.* 2004b). Extremely elevated serum ferritin levels (usually above 2,000 ng/ml) are usually indicative of true iron overload, a condition also known as haemosiderosis (Powell *et al.* 1998; Kalantar-Zadeh *et al.* 2004b). Moderately high levels of serum ferritin, i.e. up to

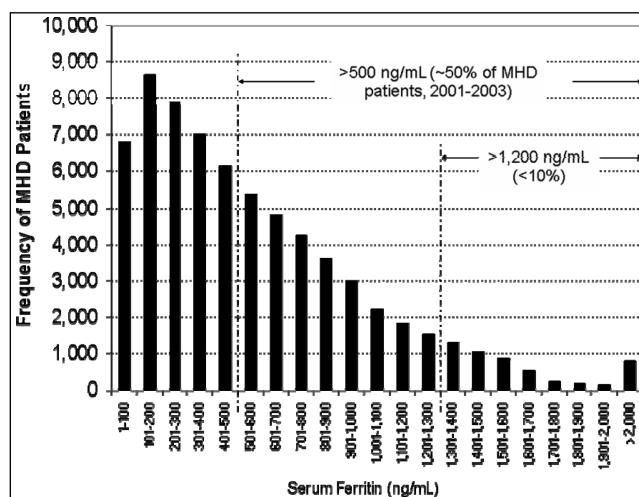


Figure 1: Distribution of serum ferritin in 58,058 MHD patients from July 2001 to June 2003 in *DaVita* dialysis clinics. Based on data from Kalantar-Zadeh *et al.* 2005b. MHD, Maintenance Haemodialysis.

2,000 ng/ml, have not been found to be associated with excessive tissue iron stores in postmortem autopsies (Gokal *et al.* 1979). Even though a recent study has indicated a mathematically significant correlation between serum ferritin and liver iron stores using the indirect imaging known as SQUID (Canavese *et al.* 2004), it appears unlikely that serum ferritin levels below 2,000 ng/ml are associated with clinically harmful increases in body iron stores.

The increase in serum ferritin during inflammation, infection, liver disease, malignancies and other non-iron-related conditions may hinder the ability to assess iron stores under the concurrent presence of these conditions. Serum ferritin is increased with malignancies such as in neuroblastoma (Blatt *et al.* 1990; Silber *et al.* 1991), renal cell carcinoma (Kirkali *et al.* 1999; Miyata *et al.* 2001) or Hodgkin lymphoma (Hann *et al.* 1990). Hyperferritinaemia is also associated with liver dysfunction, probably because the liver is the main organ to clear circulating ferritin molecules (Isa *et al.* 1988). High ferritin levels have been reported in CKD patients with glomerular disease and proteinuria (Branten *et al.* 2004). Chronic inflammation is quite common in chronic disease states such as CKD or rheumatoid arthritis (Smith *et al.* 1977), where inflammation may contribute to high ferritin levels more strongly than the actual iron content, and may even mask iron deficiency (Smith *et al.* 1977; Kalantar-Zadeh *et al.* 2001; Kalantar-Zadeh *et al.* 2003; Kalantar-Zadeh *et al.* 2004b).

In CKD, hyperferritinaemia is paradoxically associated with hyporesponsiveness to ESA and a more severe anaemia (Baillie *et al.* 1999; Gunnell *et al.* 1999). In a recent study, 34% of haemodialysis patients with elevated serum ferritin, had inflammation as the probable cause of the increased ferritin level (Kirchbaum 2001; Kirschbaum 2002). In another recent observational study in 82 haemodialysis patients, those with a serum ferritin greater than 800 ng/ml had a significantly higher CRP level and a worse Malnutrition-Inflammation Score (MIS) compared to patients with a serum ferritin below 800 ng/ml (Kalantar-Zadeh *et al.* 2004b). Multivariable models showed that both CRP and TSAT, independent of each other, correlated significantly with serum ferritin. These findings imply that a moderately high serum ferritin is not just a mere marker of iron stores but also an indicator of inflammation and/or malnutrition as well as other non-iron-related conditions in CKD patients (Kalantar-Zadeh *et al.* 2004b).

### WHAT IS THE OPTIMAL IRON LEVEL?

Optimal iron level is one that allows unhindered erythropoiesis without inducing harmful effects related to iron overload. Therapeutic administration of IV iron bypasses the body's regulatory mechanisms of iron level, thus reliable monitoring of such levels is essential in order to avoid iron overload. Unfortunately, the determination of such optimal levels is made difficult by the above mentioned problems with available diagnostic tests. Short of better monitoring tools, we need to address these issues of efficacy and safety as they relate to the levels of our commonly applied diagnostic tests (TSAT and serum ferritin). Observational studies and clinical trials have indicated that optimal erythropoiesis in patients on Maintenance Haemodialysis (MHD) occurs at a TSAT between 30–50% and a serum ferritin level as high as 1200 ng/ml (Besarab *et al.* 2000; Kalantar-Zadeh *et al.* 2007). Addressing the scenario of low TSAT accompanied by high serum ferritin, a randomised controlled trial showed that administration of IV iron to anaemic patients with a TSAT of <25% and a serum ferritin between 500–1200 ng/ml resulted in better erythropoiesis compared to no iron administration, with no short-term adverse effects (Coyne *et al.* 2007).

In spite of the better erythropoiesis seen with higher ferritin levels, such levels may appear unsafe on the long run in light of studies showing an association between dialysis morbidity, including risk of infection and iron overload reflected by a high serum ferritin (Eschbach and Adamson 1999). Observational studies have reported an association between higher ferritin and mortality in MHD patients (Kalantar-Zadeh *et al.* 2001), but subsequently adjusting for markers of malnutrition and inflammation showed that serum ferritin levels between 200 and 1,200 ng/ml and TSAT values between 30–50% were associated with the lowest all-cause and cardiovascular death risk (Kalantar-Zadeh *et al.* 2005b). Hence, the previously observed associations between moderately high levels of serum ferritin and mortality in unadjusted and case-mix adjusted models appear to be mostly due to the above detailed confounding effects of malnutrition and inflammation. Regarding associations of other markers of iron stores with long-term outcomes, a recent epidemiologic study in 1,283 haemodialysis patients showed that a low, rather than a high, serum iron was significantly associated with higher mortality and hospitalisation (Kalantar-Zadeh *et al.* 2004a), and low total iron binding capacity was shown to be associated both with iron deficiency and with increased mortality in maintenance haemodialysis

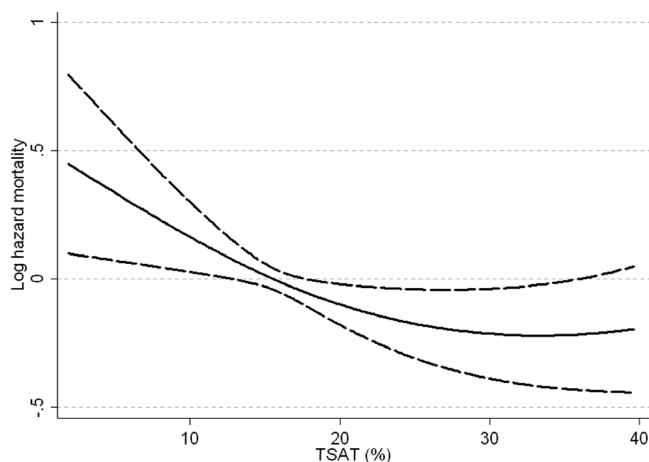


Figure 2: All-cause mortality hazard (95% confidence intervals) associated with various levels of transferrin saturation ratio in patients with moderate and advanced non-dialysis-dependent chronic kidney disease. Based on data from Kovesdy et al. 2009.

patients (Bross et al. 2009). Similar findings were reported in a study examining outcomes associated with TSAT and ferritin levels in male U.S. veterans with moderate and advanced non-dialysis-dependent CKD, in that TSAT <25% was associated with a significant increase in all-cause mortality (Figure 2) (Kovesdy et al. 2009). Higher serum ferritin levels were associated with a trend towards increased mortality (Figure 3), but when taking into account concomitant TSAT and ferritin levels, low TSAT was associated with higher mortality even in patients with elevated serum ferritin (Kovesdy et al. 2009). The same study also examined associations between iron stores and the progression of CKD, and found a significant association between higher TSAT and steeper slopes of estimated glomerular filtration rate, indicating the potential for deleterious renal effects of elevated iron levels (Kovesdy et al. 2009). These latter associations were, however, limited to patients with markers of an activated inflammatory system, suggesting that the deleterious renal effects may have been the result of chronic inflammation (which has been linked to more significant progression of CKD in earlier studies (Rao et al. 2007; Yilmaz et al. 2007), instead of a direct affect of higher tissue iron stores (Kovesdy et al. 2009).

How can we then reconcile the apparent discrepancy between data suggesting a detriment from higher iron levels on the one hand, and studies indicating beneficial outcomes in patients with substantially higher iron levels on the other? One possible explanation is the imperfect nature of our diagnostic tests

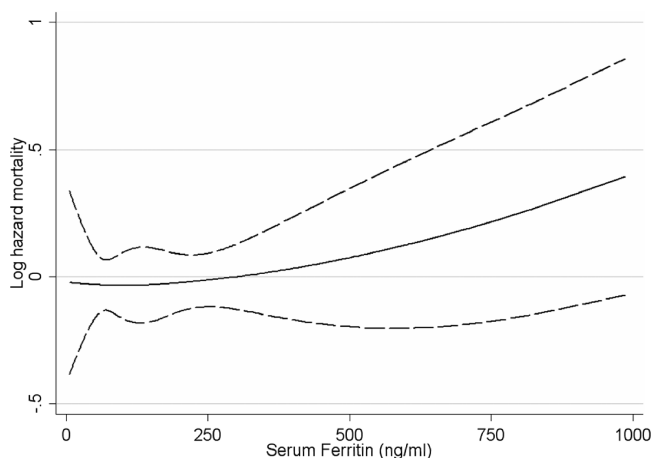


Figure 3: All-cause mortality hazard (95% confidence intervals) associated with various levels of serum ferritin level in patients with moderate and advanced non-dialysis-dependent chronic kidney disease. Based on data from Kovesdy et al. 2009.

(especially ferritin) as markers of iron excess, since the higher morbidity and mortality seen with elevated iron indices may be due to non-iron-related factors. Thus, considering high ferritin levels as the primary cause of increased mortality in the setting of inflammation or infection and preventing optimal anaemia management with IV iron for serum ferritin levels greater than 500 ng/ml (Locatelli et al. 2004) or 800 ng/ml (National Kidney Federation 2001) may be irrational (Dukkipati & Kalantar-Zadeh K. 2007). Another potential reason for the discrepancy is a difference between the various studied patient populations. Studies examining the detrimental effects of iron on cardiovascular outcomes have indicated a significant interaction with the age of the study population, with a benefit from lower iron being more significant in younger patients (Sullivan 1981; Haidari et al. 2001; Ramakrishna et al. 2003; Zacharski et al. 2007). It has been suggested that excess iron may be more important in the early stages of the atherosclerotic process, but less so in later stages or in patients with established disease (Zacharski et al. 2007). Since the vast majority of MHD patients already suffer from advanced cardiovascular disease (US Renal Data Systems 2006b), excess iron may be less relevant to this process, and it may thus be beneficial overall through allowing optimal erythropoiesis.

#### IRON REPLACEMENT: TO DO, OR NOT TO DO?

Iron replacement has become an integral part of the chronic anaemia management of patients with MHD, but there still appears to be a fear to administer higher amounts of iron,

IV Iron product, manufacturer	Molecular structure, molecular weight (MW)	Dosing <sup>a</sup>	Potential Advantages	Potential Disadvantages
Iron dextran INFeD, Watson Pharmaceuticals in USA, Cosmofer <sup>®b</sup> , Pharmacosmos in Europe Dexferrum American Regent Labs, in USA	Iron (III) hydroxide dextran complex. MW: 96–265 kDa	Maximum dose 20 mg/kg body weight by infusion over 4–6 hours. Test Dose required (UK)	Allows high doses (>1000 mg) to be administered at one time. May be administered IM (UK)	Amongst the IV iron products it has the higher potential possibility of causing life threatening anaphylactic-type reactions. Requirement for test dose. Only supplied in ampoules in Europe. Lengthy administration time compared to newer products.
Iron gluconate (Ferrlecit <sup>®c</sup> ) Watson Pharmaceuticals, in USA. Not licensed for use in UK	Sodium ferric gluconate complex in sucrose injection MW: 38 kDa	Not licensed for use in UK. Maximum dose 62.5 mg in some European countries.		Potential oversaturation of transferrin and free iron associated toxicity possible. Low maximum dose limits suitability to HD patients.
Iron sucrose (Venofer <sup>®</sup> ) American Regent Labs. (via Vifor in Switzerland) in USA. Vifor Pharma. in Europe	Iron(III) hydroxide sucrose complex. MW: 43 kDa	Maximum dose up to 200 mg, test Dose required in UK.	Most widely prescribed IV iron world wide with substantial evidence base across many therapy areas.	Potential oversaturation of transferrin and free iron associated toxicity possible. Only supplied in ampoules in Europe. Requirement for test dose in UK. Maximum dose may necessitate repeated visits in PD & ND-CKD patients
Ferumoxytol (Feraheme <sup>®</sup> ) Amag Pharmaceuticals, in USA only. Not yet licensed in Europe	Semisynthetic, ultrasmall superparamagnetic iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating. MW: 750 kDa	Maximum dose 510 mg, rapid IV injection (30 mg/second) followed by a second 510 mg injection 3 to 8 days later. For HD, PD and ND-CKD (USA)	Rapid dosing potentially allows for increased clinic throughput. Supplied in vials. No test dose required	Can be used as IV contrast material. Recently launched so consequently evidence is limited
Iron carboxymaltose (Ferinject <sup>®</sup> ) Vifor Pharma, Switzerland, licensed in much of Europe though not USA.	Macro molecular iron(III)-hydroxide carbohydrate complex. MW 150 kDa	Maximum dose <1000 mg over 15 minutes by infusion (max dose 15 mg/Kg) weekly. Up to 200 mg by bolus injection up to three times/week. (UK)	Rapid dosing potentially allows for increased clinic throughput. Supplied in vials. No test dose required	Recently launched so consequently evidence is limited

Table 2: IV iron preparations currently available in Europe and USA.

<sup>a</sup>Licensing varies considerably in countries and localities, in terms of dosing, administration and indication by market. <sup>1b</sup><http://www.pharmacosmos.com/> for the description of Cosmofer<sup>®</sup>.

<sup>2c</sup><http://www.ferrlecit.com/> for the description of Ferrlecit<sup>®</sup>.

Prescribers should always consult the product data sheet relevant to the market prior to use.

The description of Venofer<sup>®</sup> and Ferinject<sup>®</sup> comes from the product monographs and all dosing is taken from the relevant data sheets.

even when this could result in superior therapeutic efficacy. There are multiple reasons for this so-called “iron apprehension,” which is due mostly to concerns about the safety of the specific agent employed (shown in Table 2), or the amount of iron administered.

**SHORT-TERM ADVERSE REACTIONS**

Short-term adverse reactions associated with IV iron administration can be in the form of hypotension, nausea, vomiting or diarrhoea. The most severe reactions are anaphylactic or anaphylactoid reactions, which could present with rash, urticaria, laryngeal oedema or hypotension. Such reactions appear to be more common with iron dextran (~0.6%), due to the antigenicity of the dextran component (Fishbane 2003). In order to minimise severe outcomes from the administration of iron

dextran, the approved US Food and Drug Administration (FDA) label requires a test dose to be administered prior to the full therapeutic dose and patients need to be carefully monitored during the infusion. The absence of a dextran component in other IV iron products has resulted in a significantly lower incidence of life-threatening events related to these products, and a test dose does not need to be administered when using such agents in the United States (Michael *et al.* 2002; Chertow *et al.* 2006).

**IRON OVERLOAD**

In the pre-ESA era, there were frequent reports about the risk and consequences of iron overload as a result of blood transfusion or iron administration to anaemic dialysis patients (Bregman & Gelfand 1981; Waterlot *et al.* 1985). Due to ESA

administration and possibly to ongoing blood loss in patients with CKD this phenomenon is nowadays extremely rare. Correlating serum markers with tissue iron stores can be difficult, but it is likely that true tissue iron overload occurs at serum ferritin levels above 2000 ng/ml (Gokal *et al.* 1979). When adhered to, our present practice recommendations make it unlikely that such elevated levels are reached as a result of iron replacement therapy (European Renal Assoc./European Dialysis and Transplant Assoc. 2006a).

### INFECTIONS

A clinical trial performed almost 3 decades ago amongst 137 iron deficient individuals in Somalia showed that the risk of infection in those who received iron supplementation was almost 5 times higher than those who received placebo (Murray *et al.* 1978), and a limited number of observational studies have indicated an association between high serum ferritin and infection (Waterlot *et al.* 1985; Seifert *et al.* 1987). The IV replacement route delivers iron directly to the circulation, thus bypassing the natural route of iron ingestion (Fishbane 2003). Release of iron into the circulation can support the growth of bacteria, which can increase the risk of infection and potentially worsen its outcomes. It is important to note that to date, no randomised controlled study has substantiated the risk of increased infection as a result of IV iron administration in dialysis patients (Hoen *et al.* 2002; Sirken *et al.* 2006). Nevertheless, it is recommended to exercise caution when using IV iron therapy in patients with established infections, and it is probably prudent to withhold such therapy in patients with severe bacterial infections.

### OXIDATIVE STRESS

Free elemental iron is a very potent oxidising agent, and it can generate toxic free radicals. Several in-vitro studies have indicated the association between iron supplementation and oxidative stress in cell cultures (Zager *et al.* 2002; Zager *et al.* 2004). Short-term studies in dialysis patients have also showed an increase in markers of oxidative stress after IV iron administration (Michelis *et al.* 2003; Agarwal *et al.* 2004), but it is unclear what the longer term consequences of such chemical alterations are. Release of labile-free iron appears to be more likely with the smaller molecular-weight nondextran iron formulations, thus these products (iron sucrose and iron gluconate) need to be administered in smaller doses and as a slow IV infusion (Van Wyck *et al.* 2004). There may also be differences between the latter two products in their propensity to

induce tissue damage, as shown in a recent study that examined renal injury (proteinuria and enzymuria) occurring with the administration of a single dose of the two different products in patients with CKD stages 3 and 4 (Agarwal *et al.* 2007). The administration of iron sucrose was associated with a higher protein/creatinine ratio compared to iron gluconate, but there was no difference between the two agents in N-acetyl-beta-D-glucosaminidase/creatinine ratio (Agarwal *et al.* 2007). The relevance of these results to longer term administration of either agent is unclear.

### LONG-TERM SAFETY OF IV IRON ADMINISTRATION

While in vitro studies are important in clarifying the mechanisms of various adverse effects related to IV iron preparations, and short-term clinical studies are essential to prove their efficacy and safety from a regulatory standpoint, the ultimate question remains the long-term safety of these treatments as measured by their effects on survival and other relevant clinical end points. No randomised controlled study has been conducted to assess the risk of increased infection or death as a result of IV iron administration in dialysis patients. When examining a surrogate end point of adverse outcomes, a recent clinical trial showed that in those dialysis patients who received IV iron, the level of the inflammatory cytokine TNF- $\alpha$  was in fact decreased when compared to those who did not receive any IV iron (Weiss *et al.* 2003). The association between iron administration and long-term outcomes has been examined in observational studies. In a study of 10,169 haemodialysis patients in the United States, a tendency towards higher death risk was described in those patients who received higher doses of IV iron (Feldman *et al.* 2002). The same group of authors revised their initial conclusions when they used time-varying marginal structural models (which adjusted for bias by indication) to reanalyse the risk of death associated with iron administration in 32,566 haemodialysis patients (Feldman *et al.* 2004). In this latter study, there was no association between mortality and the amount of iron administration. A more recent epidemiological study in 58,058 haemodialysis patients found that, compared to those who did not receive any IV iron, administered IV iron up to 400 mg/month was associated with improved survival (Kalantar-Zadeh *et al.* 2005b). Although patients who received IV iron had significantly different demographic, clinical and laboratory features at baseline, the survival benefits of IV iron was relatively consistent in different subgroups of haemodialysis patients, including those who had high ferritin but low TSAT values (Kalantar-Zadeh *et al.* 2005b).



These findings appear to be inconsistent with the notion that the administration of IV iron is deleterious. Furthermore, a recent epidemiologic study suggested that the negative outcomes associated with higher targeted haemoglobin levels in several randomised controlled trials of ESA administration may have been the result of the relative thrombocytosis caused by the iron deficiency induced by higher doses of ESA (Streja *et al.* 2008). The merit of this hypothesis needs to be tested in clinical trials examining the concomitant administration of ESA and iron.

### CONCLUSIONS

Treatment of anaemia of CKD involves an integrated approach that addresses the complex aetiology of this entity. Iron replacement is an important component of this treatment strategy and involves routine monitoring of iron stores and replacement of iron in order to assure unhindered erythropoiesis. Flaws inherent of our routine clinical monitoring tools make it difficult to accurately assess iron stores; hence the safe and effective application of iron replacement therapy necessitates a detailed understanding of the caveats in our diagnostic methods. Optimal erythropoiesis appears to occur with an ISAT of 30–50% and a serum ferritin of up to 1200 ng/ml, and iron overload is unlikely within these ranges. Safety concerns related

to the various products used for IV iron replacement include allergic type reactions and the generation of free reactive iron in blood with consequent oxidative stress, worsened infections and tissues damage. These problems may mar the various commercially available products to a different extent. There is currently, no evidence to indicate that the adverse effects noted in-vitro and in short-term studies of IV replacement therapy are associated with deleterious long-term clinical outcomes in dialysis patients.

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### CONFLICT OF INTEREST

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