Anemia management in chronic kidney disease: Intravenous iron steps forward

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In this issue of the *American Journal of Hematology,* Lu et al. at the Food and Drug Administration (FDA) review evidence supporting the 2009 approval of ferumoxytol (Feraheme, Advanced Magnetics, Boston, MA), an injectable iron formulation, for treatment of iron deficiency anemia in patients with chronic kidney disease (CKD) [1]. Elsewhere, Unger et al. [2] at FDA have called for a reappraisal of erythropoiesis stimulating agent (ESA) use in CKD, noting a higher Hgb via ESA leads to only marginal improvements in quality of life (QoL), but increases risk of stroke, heart failure, and death. These publications highlight several important issues related to anemia management.

The medical community should welcome and encourage the FDA publications. They provide assessment of comprehensive safety and efficacy data, portions of which may not be published elsewhere. Although such data have long been available at the FDA website, review articles rarely reference this information. Some clinical guidelines are developed based solely on peer-reviewed publications, encouraging pharmaceutical companies to publish only the most favorable trial results and positive interpretations of data. Lu's [1] article presents all important ferumoxytol trial information in a peer-reviewed setting and provides the FDA's considered viewpoint.

Unger and coworkers note that recent trials of ESAs in CKD populations demonstrate serious safety issues, including increased risk of stroke, thrombosis, heart failure, and death [2]. They state "It remains to be shown in a controlled trial that assignment to any higher (hemoglobin; Hgb) target...or to ESA dosing regimens necessary to attain these targets prevents cardiovascular events or indeed does not increase their likelihood." Trials of IV iron have used increased Hgb as a surrogate endpoint for improved clinical outcomes. Ferumoxytol, like the four other IV iron products (Table I), was approved for use based on Hgb efficacy and short-term safety data.

As with all IV iron products, ferumoxytol is an iron oxide particle with a carbohydrate shell [3]. Uniquely, ferumoxytol has a polyglucose sorbitol carboxymethylether coating, and the lowest free iron release measured in in vitro studies of iron products [4]. Free iron is thought to be responsible for many adverse events observed following intravenous iron administration. Ferumoxytol is approved for rapid injection (17 to 60 sec) of a relatively large dose of iron (510 mg), which can be repeated 3 to 8 days later. As noted by Lu et al. and the FDA approved packaging information, patients should nevertheless be monitored for at least 30 min following each injection [1,5]

Oral iron, the primary treatment for iron deficiency, is limited by poor tolerability because of gastrointestinal side effects and resulting problems with compliance. In addition, in many patients oral iron is not easily absorbed and does not replace iron stores rapidly enough to meet iron losses. Oral iron is contraindicated in inflammatory bowel disease [6].

While ferumoxytol was compared with oral iron or saline injections, none of the registry trials for IV iron products have used other forms of IV iron as comparators [3,7,8]. Four other IV iron products are available in the US: two with dextran shells (INFeD and Dexferrum), and two with nondextran shells [ferric gluconate (Ferrlecit) and iron sucrose (Venofer)]. Each iron product is taken up into the reticuloendothelial system, where the shell is degraded for iron to be bioavailable. Although the efficacy of IV iron is directly related to the amount of iron administered, iron products vary in their molecular weight, pharmacokinetics, effects on oxidative markers, propensity for inducing hypophosphatemia, and propensity to cause transient proteinuria following administration [4,9–12]. Consequently, there could be differences in both efficacy and safety among products.

Although more than 15 years of continuous use of IV iron in dialysis patients has not led to clear evidence of harm, potential adverse effects might only be apparent in randomized trials, as with ESAs [2,13]. We lack large clinical trials comparing the long term safety of IV iron products to each other, or comparing small doses to large doses. Although both Dexferrum and INFeD are iron dextrans, Dexferrum causes many more serious reactions [14]. In 1997, INFeD briefly became unavailable, leading to widespread change to Dexferrum in dialysis patients. During this period there was a 1100% increase in the number of serious adverse events with IV iron reported to the FDA (Freedom of Information, FDA). Subsequently, numerous publications have reported significantly more adverse reactions with Dexferrum, the National Comprehensive Cancer Network recommends against the use of Dexferrum, and FDA has altered Dexferrum labeling to warn that it is not clinically interchangeable with INFeD [14,15].

The nondextran IV irons, ferric gluconate and iron sucrose, approved in 1999 and 2000, respectively, quickly replaced iron dextran in dialysis patients, because they were thought to be safer, though we lack rigorous comparative trials to support this viewpoint. These products have a low incidence of anaphylactoid reactions, but do lead to hypotension and gastrointestinal symptoms when doses exceed 200–300 mg, necessitating repeated doses to correct iron deficiency [3].

As Lu's analysis indicates ferumoxytol, like all IV preparations, has been reported to cause anaphylactoid reactions [1]. With the exception of Dexferrum, the acute safety differences among IV iron products are small and clinically irrel-

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TABLE I. Intravenous Iron Preparations with Common Dosing Regimens

Product generic (brand name)	Approved maximum dose	Commonly employed maximum dose	Dose-related reactions
Ferumoxytol (Feraheme®)	510 mg over 17 sec	Same	None reported
Iron dextrans (INFeD, Dexferrum®)	100 mg over 2 or more minutes	1000 mg over 2 – 4 h (requires test dose)	Arthralgias
Ferric gluconate (Ferrlecit®)	125 mg over 5 – 10 min	250 mg over 2 – 3 h	Hypotension, edema
Iron sucrose (Venofer®)	200 mg over 2 – 5 min	300 mg over 2 – 3 h	Hypotension, edema

evant when deciding which agent to use, though comparator trials are needed to be certain [16].

Ferumoxytol may offer convenient advantages over other preparations in the non-dialysis setting (Table I). Repeated doses of iron sucrose and ferric gluconate are required to provide 1 g iron loading. INFeD can be administered as a total dose infusion over several hours after a test dose. One of us (MA) has trialed 1 g INFeD infusions over 1 hr, potentially challenging the apparent convenience of ferumoxytol [17].

Among IV iron products, ferumoxytol uniquely possesses superparamagnetic properties, rendering it a (FDA unapproved) contrast agent for magnetic resonance imaging (MRI) [3]. Ferumoxytol taken into the reticuloendothelial system will alter the MRI image for days to weeks. This property can be viewed as an advantage or disadvantage for use of ferumoxytol.

Iron therapy improves CKD-related anemia and can obviate or reduce the need for ESAs [18–20]. Similarly, randomized trials in oncology have shown IV iron enhances Hgb response to ESA, and may reduce the dose and duration of ESA therapy [19]. Ferumoxytol significantly increased Hgb in both ESA-treated and untreated patients with CKD [17,21].

The recent TREAT study in 4038 diabetics with CKD-related anemia showed the ESA, darbepoetin, failed to reduce cardiovascular events or deaths, or provide significant QoL benefits compared with placebo treatment [22]. Those randomized to darbepoetin had almost double the risk of stroke, and a disturbing trend toward recurrence of cancers and subsequent cancer deaths. Patients in both arms received oral iron (69% of subjects), while 20.4% of placebo-treated patients received IV iron compared with 14.8% in the darbepoetin arm ($P < 0.001$). Mean Hgb in the placebo arm slowly increased from 10.4g/dL to ~10.8 g/dL at 2 years despite progressive CKD and use of ESA only while Hgb was below 9.0 g/dL [22]. The changes in Hgb in the placebo arm of the TREAT trial, and the ferumoxytol efficacy data, suggest that iron deficiency plays a much larger role in CKD-related anemia than generally believed.

Widespread oral iron and IV iron for CKD–related anemia may obviate the need for ESAs in many patients, and although there has been no substantive negative signal in published studies to date, large long-term trials assessing the safety of iron in CKD and oncology are needed. Toward this end, Anker and colleagues performed a 6 month randomized trial of repletion doses of IV iron (ferric carboxymaltose) vs. placebo in 459 patients with NYHA Class II or III heart failure [23]. Almost half the patients had Stage 3 CKD (eGFR <60). IV iron repletion increased Hgb and significantly improved symptoms, functional capacity, and QoL. Contrary to concerns expressed by ESA supporters, IV iron did not increase mortality (3.4 vs 5.5% with placebo), first hospitalization (17.7 vs 24.8% with placebo), or infection rates. While larger and longer trials are needed, Anker's trial supports the view that IV iron treatment of iron deficiency provides clinical benefits beyond an increased Hgb. That is what the FDA wants to see, and clinicians want to accomplish.

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Everolimus in relapsed Hodgkin's lymphoma: Something exciting or a case of caveat mTOR?

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Hodgkin's disease (HD) is a rare form of cancer that predominantly affects young people with an incidence of ~3/100,000 in the western World. Since the advent of combination chemotherapy [1], this has proven to be a highly curable disease; however, a significant number of patients presenting with HD will ultimately die from it. This includes young patients relapsing after salvage chemotherapy and transplantation and a proportion of elderly patients for whom conventional chemotherapy is not appropriate or well tolerated and where different approaches are needed. In this issue of the *American Journal of Hematology*, Johnston et al. [2] describe the first clinical trial of the mammalian target of rapamycin (mTOR) inhibitor everolimus in patients with relapsed/refractory HD.

Sirolimus (rapamycin) is a macrolide antibiotic that was developed and subsequently licensed as an immunosuppressive agent for use in solid organ transplantation. As part of the National Cancer Institute's Cancer Therapeutics Evaluation Programme (CTEP), rapamycin was shown to have antitumor effects demonstrable against a range of malignancies. Although the variable bioavailability of this agent made it pharmacologically unsuitable to be taken any further as an anticancer agent, a number of novel analogs [temsirolimus (CCI-779), everolimus (RAD 001), and deforolimus (AP 23573)] have been developed. These drugs work through inhibition of the mTOR. This is a serine/threonine kinase that has a key role in regulating cell cycle progression, cellular growth and protein synthesis through interactions with a number of signaling pathways including phosphatidylinositol 3-kinase (PI3K)/AKT, bcr/abl, ras, TCL1, and membrane receptor tyrosine kinases [3]. The PI3K/Akt/mTOR pathway is heavily dysregulated in hematological malignancies, including Hodgkin's disease [4] and provides a rationale for the use of mTOR inhibitors.

All of the three mTOR inhibitors have been trialed in various cancers [5] with the most extensive experience involving intravenous temsirolimus [6]. The phase I studies with temsirolimus demonstrated activity in renal cell carcinoma [7,8] and subsequent studies lead to its licensing for this indication [9]. In mantle cell lymphoma (MCL), two phase II trials demonstrated response rates of around 40% [10,11] and a subsequent large randomized phase III trial showed a significant PFS advantage for temsirolimus over investigator choice single-agent chemotherapy. This led on to a European license for this indication but the response rate in this multicenter trial was only 22% [12]. In common, everolimus has a license in relapsed renal cell carcinoma [13] and in vitro appears active against MCL [14]. A phase II single-agent study in this disease is ongoing in Europe.

Johnston and colleagues describe the first trial of an mTOR inhibitor in Hodgkin's disease. This was a single-center phase II trial that evaluated a total of 19 patients as part of a larger study evaluating this drug in rarer forms of lymphoma. This was a representative population with a median age of 37 years, who were heavily pretreated (median number of prior therapies of six) and where the median TTP for their last therapy was 4 months. Using a daily oral dose of 10 mg the observed ORR was 47% with a median duration of response of 7.1 months. This included one CR and four patients remain progression free at 12 months with one patient remaining on drug for more than 3 years. However, 74% patients experienced grade III/IV toxicity and half of all patients required dose reductions. While hematological toxicity predominated, five patients (25%) experienced significant pulmonary toxicity, a side effect that has previously been observed in other studies involving both everolimus [15] and temsirolimus [12].

Where does this take the therapy of HD? This study suggests that everolimus is an active agent in this disease but this requires further evaluation in a multicenter setting. The difference in observed response rates with temsirolimus in mantle cell lymphoma between the phases II and III settings certainly warrant some caution. However, within the larger trial of everolimus in rarer lymphomas, the efficacy in CLL/SLL (response rate of 18%) [16] is clearly inferior to that seen in HD suggesting this to be a suitable disease in which to explore this compound further. There is a real need for agents that can be given to patients who have exhausted conventional options in this disease and an oral agent is advantageous especially for the elderly patients. In one population-based study of patients more than 60 years presenting with HD, almost half of the patients died from progressive disease and almost all patients more than 70 years did, even if it was localized at presentation [17]. The toxicity observed in the study from Johnston would be a cause for concern when expanding that experience to an older, frailer cohort of patients where arguably there is a greater need for such agents. If the response rates observed with everolimus are verified then a move to combination therapy would be the obvious next stage; however, the unexplained pulmonary toxicity seen here, which has also been observed previously in renal cell carcinoma, suggest that caution should be observed [18]. Despite the fact that the FDA has not approved any new drug for HD in 30 years, there are a number of promising agents in development, including HDAC inhibitors, lenalidomide, anti-CD30, and other antibodies [19]. While phase II single-agent studies are a good place to start, it is essential that promising agents are moved into randomized phase III trials that compare them against established therapeutic options before they can safely and confidently moved into the clinic.

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