Safety and Effectiveness of Ferumoxytol in Hemodialysis Patients at 3 Dialysis Chains in the United States Over a 12-Month Period

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ABSTRACT

Background: Intravenous (IV) iron is the treatment of choice for iron-deficiency anemia (IDA) in patients with dialysis-dependent chronic kidney disease (DD-CKD). However, IV iron products have been associated with serious adverse events (SAEs), including anaphylactoid reactions. Ferumoxytol is an IV iron preparation that can be injected over a short period of time. Although randomized clinical trials support ferumoxytol's efficacy and safety, additional insights may be drawn from the acquisition of long-term, repeat dosing efficacy and safety data in a real-world setting.

Objective: The goal of this study was to characterize the effectiveness and safety profile of ferumoxytol as administered to adult DD-CKD patients with IDA in a real-world setting. The ability of ferumoxytol to maintain hemoglobin (Hb), transferrin saturation (TSAT), and ferritin treatment targets established by the 2006 Kidney Disease Outcomes Quality Initiative guidelines was determined in 3 medium-sized US-based dialysis chains.

Methods: This retrospective, observational study was conducted to examine laboratory and dosing data for all patients who received any dose of ferumoxytol at 3 US-based dialysis chains over a 12-month period. Investigators and/or physicians from each of the chains also made independent determinations regarding the seriousness of any adverse event (AE). Special attention was paid to the incidence and types of AEs and SAEs that were potentially associated with ferumoxytol.

Results: Over the 12-month observation period, 8666 patients (mean [SD] age in chains A, B and C, 63.9 [14.8], 63.9 [14.9] and 63.6 [15.1], respectively), were treated with 33,358 doses of ferumoxytol across the 3 chains. Treatment with ferumoxytol corresponded to an increased mean monthly Hb level relative to baseline (0.13–0.69 g/dL) and led to an increase in the proportion of patients maintained within the target Hb range of 10 to 12 g/dL (61%–72%). Ferumoxytol was also associated with increases in TSAT and ferritin that stabilized throughout the observation period. Incidence of AEs was similar across the 3 chains; between 0.07% and 1.77% of all patients treated at each chain experienced an AE associated with ferumoxytol administration. SAEs were reported in 0.2% of patients. The most common AEs reported ($\geq$6 patients) were nausea (0.37% of patients), pruritus (0.29%), vomiting (0.25%), hypotension (0.21%), and dyspnea (0.20%). Two patients (0.02%) experienced anaphylactoid reactions. The AE profile of ferumoxytol remained consistent with that reported from controlled clinical trials.

Conclusions: These long-term data, which include repeat dosing in a large number of DD-CKD patients with IDA in a real-world setting, confirm the effectiveness of ferumoxytol in increasing and maintaining Hb levels within the target range and with favorable assessments of long-term safety. (*Clin Ther.* 2014;36:70–83)

Key words: chronic kidney disease, ferumoxytol, hemodialysis, intravenous iron, iron-deficiency anemia.

INTRODUCTION

Anemia is a common complication of chronic kidney disease (CKD). It can occur at any stage of the disease

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and affects nearly all patients with dialysis-dependent CKD (DD-CKD).[1] The burden of anemia and its complications, including cardiovascular morbidity and reduced quality of life, are significant. Iron deficiency is a major cause of anemia in the DD-CKD population; causes of iron deficiency include reduced dietary iron intake or absorption, iron sequestration due to inflammatory processes, procedural blood loss, and increased red blood cell production in response to erythropoiesis-stimulating agents (ESAs).[2,3]

Management of iron-deficiency anemia (IDA) includes iron supplementation and use of ESAs. Oral iron supplementation is convenient and inexpensive but carries the risks of poor intestinal absorption and gastric adverse effects, which may affect adherence.[4] Intravenous (IV) administration of iron avoids these concerns and provides a rapidly available form of iron for red blood cell production. For patients with DD-CKD, IV iron provides a convenient treatment option because IV access will have already been established. Thus, clinical practice guidelines for the treatment of anemia in CKD, such as those issued by the National Kidney Foundation, the European Best Practice Guidelines Working Group, and the Kidney Disease: Improving Global Outcomes initiative, recommend IV iron supplementation to increase hemoglobin (Hb) levels in patients with DD-CKD.[5–7] The efficacy of IV iron administration in CKD patients has been demonstrated in a large number of randomized controlled trials, including studies comparing IV iron with oral iron, with and without ESA treatment, as reported in a recent Cochrane Review.[8] In the DD-CKD population, the established IV access and convenience of being able to administer IV iron during dialysis treatments are important factors that make IV iron an appropriate choice for iron supplementation.

Several IV iron products are currently available for the treatment of iron deficiency in CKD; the class includes iron dextran, sodium ferric gluconate, iron sucrose, iron isomaltoside, and ferric carboxymaltose.[9–13] The use of IV iron dextran has fallen out of favor in recent years due to the necessity of a test dose and the risk of anaphylactoid reactions even after a successful test dose.[14,15] The second-generation IV therapies, ferric gluconate and iron sucrose, have demonstrated a better safety profile, although iron sucrose has been associated with anaphylactoid reactions when administered by using rapid infusion at higher doses.[16,17] The release of biologically active free iron during IV administration may contribute to the development of acute and chronic adverse events (AEs).[18] Some IV iron products can be administered as a rapid and large single dose, up to and in excess of 1000 mg.[19]

Ferumoxytol is an IV iron product indicated for the treatment of IDA in adult patients with CKD. The physical properties of ferumoxytol enable tight binding of the iron moiety, thereby decreasing free iron release.[20,21] Ferumoxytol does not require a test dose, and treatment is normally initiated with a rapid IV administration (~1 minute) of a 510 mg dose.[22] It has a superparamagnetic iron oxide with a polyglucose sorbitol carboxymethyl ether coating. This carbohydrate coating is believed to reduce immunologic sensitivity and tightly bind the iron, thus limiting the release of bioactive, free iron. This structural distinction of ferumoxytol limits exposure to free iron and its toxicity, and may explain the high degree of tolerance to administration of a large IV dose of iron in a short period of time.[20] There is no requirement for a test dose; treatment can be initiated with the rapid IV administration (17–60 seconds) of a 510 mg dose, which may be repeated after 2 to 8 days. Patients should be monitored by trained staff for signs of AEs for a minimum of 30 minutes' postinjection.[22] Since receiving approval from the US Food and Drug Administration (FDA) in 2009, ferumoxytol has been marketed in the United States by AMAG Pharmaceuticals, Inc.* In June 2012, European marketing authorization was granted to Takeda Pharmaceutical Company Limited to market ferumoxytol.†

The efficacy of ferumoxytol (2 injections of 510 mg) for the treatment of IDA in adult patients with CKD has been compared with oral iron in 3 Phase III trials.[23–25] Two of the studies involved non-dialysis-dependent CKD (NDD-CKD) patients who, in both trials, were either on a stable ESA dose or were precluded from starting an ESA during the study[23,24]; the third study was conducted in patients with DD-CKD, all receiving supplemental ESA treatment.[25] In both patient populations, analysis of the mean change in Hb at day 35 for each study showed that IV iron

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†Trademark: Rienso® (Takeda Pharmaceutical Company Limited, Tokyo, Japan).