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FERUMOXYTOL: A REVIEW

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ABSTRACT

Ferumoxytol is a super paramagnetic iron oxide nanoparticle coated with a low molecular weight semi-synthetic carbohydrate. This drug is indicated for the treatment of iron deficiency anemia in adult patients who have experienced intolerance to oral iron or have experienced an unsatisfactory response to oral iron or who have chronic kidney disease (CKD). Iron deficiency anemia is a common complication in patients with chronic kidney disease (CKD). The recommended initial dose is a 510 mg intravenous injection followed by a second 510 mg intravenous injection 3 to 8 days later. Ferumoxytol is having similar effect and safety profile compared to other iron supplements. But in contrast, if patients are unresponsive or intolerant to oral iron supplements, ferumoxytol is a better choice and it does not have any serious adverse events. Ferumoxytol use can shorten the clinical visits of the patient as only two effective doses are required.

KEYWORDS: Ferumoxytol, Iron Deficiency Anemia, Chronic Kidney Disease.

INTRODUCTION

Ferumoxytol is a super paramagnetic iron oxide nanoparticle coated with a low molecular weight semi-synthetic carbohydrate. It helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

Ferumoxytol is specifically indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.

Ferumoxytol is supplied as a solution for intravenous injection. The recommended initial dose is a 510 mg intravenous injection followed by a second 510 mg intravenous injection 3 to 8 days later. Ferumoxytol should be administered as an undiluted intravenous injection delivered at a rate of up to 1 mL/sec (30 mg/sec). For patients receiving hemodialysis, administer Ferumoxytol once the blood pressure is stable and the patient has completed at least one hour of hemodialysis.

Anemia is a reduction in red blood cell (RBC) mass. It often isdescribed as a decrease in the number of RBCs per microliter (μL) or as a decrease in the hemoglobin (Hb) concentration in blood to a level below the normal physiologic requirement for adequate tissue oxygenation. Iron deficiency is a state of negative iron balance in which the daily iron intake and stores are unable to meet the RBC and other body tissue needs. Anemia of chronic disease (ACD) refers to a mild to moderate anemia that results from decreased RBC production that is associated with a number of disorders (eg: autoimmune disorders, chronic infections, chronic renal failure, andneoplastic disease).

Chronic kidney disease (CKD) is defined as any abnormality in kidney structure or function present for three months or longer, with implication for health. Anemia, which affects most patients with CKD, is caused by a decreased production of erythropoietin (EPO), a glycoprotein that stimulates red blood cell production in the bone marrow and is released in response to hypoxia.

Ferumoxytol

Indications and usage

Ferumoxytolis indicated for the treatment of iron deficiency anemia (IDA) in adult patients:

- Who have intolerance to oral iron or have had unsatisfactory response to oral iron or

•Who have chronic kidney disease (CKD)

Dosage and administration

The recommended dose of ferumoxytolis an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Administer ferumoxytol as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes. Administer while the patient is in a reclined or semi-reclined position. The dosage is expressed in terms of mg of elemental iron, with each mL of ferumoxytol containing 30 mg of elemental iron. Evaluate the hematologic response (hemoglobin, ferritin, iron and transferrin saturation) at least one month following the second ferumoxytol infusion. The recommended ferumoxytol dose may be readministered to patients with persistent or recurrent iron deficiency anemia.

Dosage forms and strengths

Ferumoxytol Injection is available in single-dose vials. Each vial contains 510 mg of elemental iron in 17 mL (30 mg per mL).

Warnings and precautions

Greater risk of anaphylaxis in patients with multiple drug allergies.

- Hypotension: Ferumoxytol may cause hypotension. Monitor for signs and symptoms of hypotension following each administration of ferumoxytol.
- Iron Overload: Regularly monitor hematologic responses during ferumoxytol therapy. Do not administer ferumoxytol to patients with iron overload.
- Magnetic Resonance Imaging Test Interference: Ferumoxytolcan alter magnetic resonance imaging (MRI) studies.

Adverse reactions

The most common adverse reactions (≥ 2%) are diarrhea, headache, nausea, dizziness, hypotension, constipation, and peripheral edema.

Mechanism of action

Ferumoxytol consists of a super paramagnetic iron oxide that is coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g: ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

Pharmacokinetics

The pharmacokinetic (PK) behavior of Ferumoxytolhas been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis. Ferumoxytol exhibited dose-dependent, capacitylimited elimination from plasma with a half-life of approximately 15 hours in humans. The clearance (CL) was decreased by increasing the dose of ferumoxytol. Volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (Cmax) and terminal half-life (t1/2) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of ferumoxytol administered intravenously within 24 hours were 69.1 mL/hr and 3.16 L, respectively. The Cmax and time of maximum concentration (tmax) were 206 mcg/mL and 0.32 hour, respectively. Rate of infusion had no influence on ferumoxytolPK parameters. No gender differences in ferumoxytolPK parameters were observed. Ferumoxytolis not removed by hemodialysis.

Ferumoxytol in Iron Deficiency Anemia

In most patients, the iron deficiency should be treated with oral iron therapy. Iron replacement therapy is essential for increasing iron stores and raising hemoglobin levels in patients with iron deficiency anemia (IDA). Oral iron supplements have limited absorption and are commonly associated with gastrointestinal (GI) side effects that reduce compliance, resulting in limited increases in hemoglobin. In patients without chronic kidney disease (CKD), oral iron therapy is frequently used to treat IDA. However, when oral iron therapy is unsatisfactory or cannot be tolerated, intravenous (IV) iron therapy may be appropriate.

In a study which compares ferumoxytol with iron dextran ferumoxytol 1.02 g, delivered as two doses of 510 mg, was shown to bewell tolerated and effective in correcting anemia in a relatively short time in adults with IDA and a history of unsatisfactory response to oral iron therapy or in whom oral iron could not be used. The safety profile of ferumoxytol was shown to be generally comparable to placebo. No serious hypotensive reactions were reported with ferumoxytol. In this study, a full 1.02g treatment course of ferumoxytol was administered with only two injections of 510 mg each in 17 mL over a short time frame (each injection took 17–60 sec), with no requirement for the administration of a test dose and no need for premedication. In contrast, boxed safety warnings for iron dextran require the administration of a test dose and there is a limitation on the daily therapeutic dose that can be administered (100 mg/day). This results in the need for multiple office visits (as many as 10 visits) and repeated IV placements to administer the typical 1g therapeutic dose of iron dextran. In contrast, ferumoxytol offers the ability to deliver the total 1.02-g dose with two clinic visits, possibly improving treatment compliance[2], efficiency, and cost savings.[3] Being able to deliver the full therapeutic course in two doses also has the potential to reduce patient exposure to the risk of AEs that exist with each individual IV administration.[1]

Few trials have examined rates of hypersensitivity reactions (HSRs) with intravenous iron formulationsused to treat iron deficiency anemia (IDA). In a study which compares ferumoxytol with ferric carboxymaltose focused on safety and efficacy of these drugs.

Ferumoxytol was noninferior to ferric carboxymaltose for both the primary (the incidence of moderate-to-severe HSRs, including anaphylaxis, or moderate-to-severe hypotension) and secondary (the incidence of moderate-to-severe HSRs, including anaphylaxis, serious cardiovascular events, and death) composite safety end points, with equivalent efficacy in raising hemoglobin despite a lower dose. The incidences of treatment emergent adverse events were similar in both groups, with no new safety signals. Severe hypophosphatemia was seen at higher rates with ferric carboxymaltose treatment.[4]

In another study which focused on the safety and efficacy of ferumoxytol concluded that no SAEs were observed or reported during the courseof this study. Other reported AEs inthis study were minor, either transient infusion-related events that necessitated no additional therapy or selflimiting arthralgias and myalgias 24–48 hour post-infusion, consistent with the minor AEs reported with other IV iron formulations. Ferumoxytol also demonstrated excellent efficacy in this population with a diverse group of etiologies for IDA.[5]

A study which compared ferumoxytol and iron sucrose concluded that transferrin saturation, quality-of-life measures, and safety outcomes were similar between the two treatment groups. Overall, ferumoxytol demonstrated comparable safety and efficacy to iron sucrose, suggesting that ferumoxytol may be a useful treatment option for patients with IDA in whom oral iron was unsatisfactory or could not be used.[6]

In general we can conclude that ferumoxytol is having similar effect and safety profile compared to other iron supplements. But in contrast, if patients are unresponsive or intolerant to oral iron supplements, ferumoxytol is a better choice and it does not have any serious adverse events.

Ferumoxytol in Chronic Kidney Disease

Chronic kidney disease is characterized by a progressive deteriorationin kidney function with time characterized by irreversible structural damage to existing nephrons. Anemia is seen in most of the CKD patients due to decreased erythropoietin synthesis. Ferumoxytol is a semisynthetic carbohydrate coated, super paramagnetic iron oxide nanoparticle recently approved in the treatment of iron-deficiency anemia of CKD.

In a study, ferumoxytol in treating iron deficiency anemia in CKD is evaluated and concluded that ferumoxytol significantly increased hemoglobin compared with oral iron. Ferumoxytol was generally well tolerated compared with oral iron. Most adverse events were mild to moderate in intensity.[7]

In a study which compared ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD the adverse event profiles of the two regimens were fairly similar. Ferumoxytol-treated patients were shown to have an earlierincrease in mean Hb compared with patients treated with iron sucrose. IV iron is the recommended route of administration for thetreatment of Iron Deficiency Anemia in CKD patients on hemodialysis andnondialysis CKD patients who have failed a course of oraliron to allow an adequate iron supply to support erythropoiesis.[8]

In a study which evaluated the safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients, administration of ferumoxytol can be safe and effectivein increasing iron storesby improving ferritin and transferrin saturation, and in raising hemoglobin levels inanemic CKD patients and is well tolerated at a rapid infusionrate. This study also demonstrates that ferumoxytol can be administeredas a rapid bolus of 30 mg of iron per second ina concentrated form of 30 mg/mL, and in a dosage of up to510 mg, in contrast other iron supplements can be administered in lower doses but it takes longer period oftime and more clinic visits to administer equivalent doses.[9]

In another study which checked the safety and effectiveness of ferumoxytol in hemodialysis patients, concluded that ferumoxytolwas broadly effective in increasing and maintaining iron parameters and Hb values as an adjunct therapy to ESA administration for anemia therapy in dialysis patients. The study also offers confirmation that the safety profile for ferumoxytol is both predictable and manageable when used to treat Iron Deficiency Anemia inpatients with CKD.[10]

In general the use of ferumoxytol in treating anemia in CKD is a good option, but the efficacy and safety profile are almost similar when compared with other iron supplements. Serious adverse events are notmuch reported in case of ferumoxytol. Only two doses of ferumoxytol is needed and shorter clinical visits are needed.

CONCLUSION

Our review mainly focuses on the essence of ferumoxytol use in iron defiency anemia. Though, ferumoxytol have shown to be non-inferior to iron supplements in a number of studies, the major advantage of ferumoxytol lies in improving patient compliance as well as cost savings, when compared to iron. Ferumoxytol can also be used as a substituent when the patient is unresponsive or intolerant to iron supplements. In the case of anemic chronic kidney disease, ferumoxytol has shown similar effectiveness as that of iron. However, ferumoxytol use can shorten the clinical visits of the patient as only two effective doses are required. Further studies on ferumoxytol is required to acquire robust amount of evidence regarding the safety and efficacy of the drug.

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