The Efficacy of Ferumoxytol for Iron Deficiency Anemia: A Meta-Analysis of Randomized Controlled Trials

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Keywords

Ferumoxytol · Iron deficiency anemia · Hemoglobin level · Randomized controlled trials · Meta-analysis

Abstract

Introduction: This systematic review and meta-analysis aims to explore the influence of ferumoxytol versus placebo on iron deficiency anemia. **Methods:** We search for randomized controlled trials (RCTs) assessing the effect of ferumoxytol on iron deficiency anemia on PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases. This meta-analysis is performed using the random-effects model. **Results:** Four RCTs are included in the meta-analysis. Compared with the control group for iron deficiency anemia, intravenous ferumoxytol can significantly improve the proportion of patients with a ≥ 20 g/L hemoglobin (Hb) increase (RR = 18.43; 95% CI = 7.29–46.57; $p < 0.00001$), the proportion of patients with an Hb level ≥ 120 g/L (RR = 18.55; 95% CI = 8.66–39.72; $p < 0.00001$), transferrin saturation (mean difference = 11.08; 95% CI = 9.86–12.31; $p < 0.00001$) and FACIT-fatigue score (mean difference = 4.60; 95% CI = 3.21–6.00; $p < 0.00001$), but has no remarkable influence on adverse events (RR = 1.33; 95% CI = 0.84–2.10; $p = 0.22$), serious

adverse events (RR = 1.22; 95% CI = 0.74–2.02; $p = 0.44$), and death (RR = 0.32; 95% CI = 0.05–1.95; $p = 0.22$). **Conclusions:** Intravenous ferumoxytol can provide the important benefits for iron deficiency anemia.

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Introduction

Iron deficiency anemia is very common in patients, and is mainly caused by gastrointestinal diseases, chronic kidney diseases and cancers [1–5]. This anemia results from blood loss, malnutrition, malabsorption of iron, and impaired utilization of endogenous iron [6–9]. For example, approximately 43–86% of patients with iron deficiency anemia have gastrointestinal pathologies (e.g., inflammatory bowel disease, colon cancer, polyps, and mucosal damage) [10–12]. Iron deficiency anemia can substantially impair the quality of life, the ability to work, and these patients often experience fatigue, and impaired physical and/or cognitive functioning [13–15].

Oral iron supplementation is recommended as a simple and safe treatment for iron deficiency anemia, but many patients cannot take oral iron, tolerate it or respond

with an adequate replenishment of iron store [16, 17]. Ferumoxytol is a superparamagnetic iron oxide in a non-dextran, semisynthetic, carbohydrate shell composed of polyglucose sorbitol carboxymethyl ether (PSC). The PSC coating can reduce the potential toxicity through isolating bioactive iron cores from plasma components until the iron-PSC complex enters the reticuloendothelial system macrophages [18–21]. Supplemental to the original drug application, ferumoxytol is now approved for broad indication in the US for the treatment of iron deficiency anemia [22]. In addition, ferumoxytol is also approved for use in patients with chronic kidney disease-related iron deficiency anemia in the European Union.

The efficacy and safety of ferumoxytol treatment on iron deficiency anemia has been reported in several studies [22–24]. With accumulating evidence, we perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of ferumoxytol treatment on iron deficiency anemia.

Materials and Methods

The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [25].

Search Strategy and Study Selection

Two investigators have independently searched the following databases (inception: March 2018): PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: ferumoxytol, iron deficiency, and anemia. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: (i) patients with iron deficiency anemia; (ii) intervention treatments are ferumoxytol versus placebo; (iii) study design is RCT; (iv) studies are published in English.

Data Extraction and Outcome Measures

We have extracted the following information: authors, number of patients, age, gender, hemoglobin (Hb) level, transferrin saturation, and detailed methods in each group. Data have been extracted independently by two investigators, and discrepancies were resolved by consensus. We also contacted the corresponding author to obtain the data when necessary. The primary outcomes are the proportion of patients with a ≥ 20 g/L Hb increase and an Hb level of ≥ 120 g/L. Secondary outcomes include transferrin saturation, Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score, adverse events, serious adverse events, and death.

Quality Assessment in Individual Studies

The methodological quality of the included studies is independently evaluated using the modified Jadad scale [26]. There are 3

Fig. 1. Flow diagram of the study searching and selection process.

items for the Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). One point would be allocated to each element if they have been mentioned in the article, and another point would be given if the methods of randomization and/or blinding have been appropriately described. If the methods of randomization and/or blinding are inappropriate, or dropouts and withdrawals have not been recorded, then one point is deducted. The score of the Jadad scale varies from 0 to 5 points. An article with a Jadad score ≤ 2 is considered to be of low quality. If the Jadad score is ≥ 3 , the study is considered to be of high quality [27].

Statistical Analysis

We estimate the mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (transferrin saturation and FACIT-fatigue score) and risk ratio (RR) with 95% CI for dichotomous outcomes (proportion of patients with a ≥ 20 g/L Hb increase and an Hb level ≥ 120 g/L, adverse events, serious adverse events, and death). The random-effects model is used regardless of heterogeneity. Heterogeneity is evaluated by the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [28]. Whenever significant heterogeneity is present, we search for the potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (<10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature Search, Study Characteristics, and Quality Assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 629 potentially relevant articles are identified initially. 629 publications are searched after the initial search of databases. 204 duplicates and 418 papers

Fig. 2. Forest plot for the meta-analysis of the proportion of patients with a ≥ 20 g/L Hb increase.

Table 1. Characteristics of included studies

First author	Ferumoxytol group						Control group						Cause	Follow-up	Jada scores
	n	age, years	female, n	Hb level, g/L	transferrin saturation, %	methods	n	age, years	female, n	Hb level, g/L	transferrin saturation, %	methods			
1 Vadhan-Raj [23], 2017, USA	75	58.5±14.1	56	90±8	9.4±10.7	intravenous 510 mg dose of ferumoxytol at the baseline visit (day 1), followed by a second dose 2–8 days later (week 1)	10	53.4±14.0	8	88±11	9.6±7.3	matched placebo	cancer	5 weeks	4
2 Ford [22], 2016, Canada	173	47.4±16.85	136	89±8.9	6.5±12.97	intravenous 510 mg dose of ferumoxytol at the baseline visit (day 1), followed by a second dose 2–8 days later (week 1)	58	52.1±15.93	44	87±7.3	4.7±3.53	matched placebo	gastro-intestinal disorders	5 weeks	5
3 Vadhan-Raj [24], 2014, USA	608	44.8±13.82	66	89±8.9	7.0±12.9	intravenous ferumoxytol 510 mg (17 mL) administered as a rapid intravenous injection in under 1 min at baseline (day 1), with a second dose 2–8 days later	200	46.0±13.58	22	88 ±8.9	5.4±4.9	matched placebo	unknown	5 weeks	5
4 Singh [29], 2008, USA	713	64.2±14.5	–	11.3±0.9	15.1±8.5	intravenous ferumoxytol 510 mg on day 0 and the alternate agent on day 7	711	63.0±15.1	–	11.3±0.9	15.1±8.6	matched placebo	chronic kidney disease	7 days	3

are excluded after checking the titles/abstracts. 3 studies are removed because of the study design and 4 RCTs are ultimately included in the meta-analysis [22–24, 29].

The baseline characteristics of 4 eligible RCTs are summarized in Table 1. The 4 studies are published between 2008 and 2017, and sample sizes range from 85 to 1,424. The standard dose of ferumoxytol is intravenous 510 mg at the baseline visit, followed by a second dose 2–8 days later. The causes of iron deficiency anemia include cancer, gastrointestinal disorders, and chronic kidney disease.

Among the 4 studies included here, 2 studies report the proportion of patients with a ≥ 20 g/L Hb increase, the proportion of patients with an Hb level ≥ 120 g/L, transferrin saturation, and FACIT-fatigue score [22, 24], 4 studies report adverse events, serious adverse events [22–24, 29], and 2 studies report death [23, 24]. Jadad scores

of 4 included studies vary from 3 to 5, and all 4 studies are considered to be high-quality ones according to quality assessment.

Primary Outcomes: The Proportion of Patients with a ≥ 20 g/L Hb Increase and an Hb Level ≥ 120 g/L

These outcome data are analyzed with the random-effects model, and the pooled estimate of the 2 included RCTs suggested that compared to the control group for iron deficiency anemia, intravenous ferumoxytol can significantly improve the proportion of patients with a ≥ 20 g/L Hb increase (RR = 18.43; 95% CI = 7.29–46.57; $p < 0.00001$), with low heterogeneity among the studies ($I^2 = 26\%$, heterogeneity $p = 0.24$) (Fig. 2).

Consistently, intravenous ferumoxytol is associated with a substantial increase in the proportion of patients with an Hb level ≥ 120 g/L for iron deficiency anemia

Fig. 3. Forest plot for the meta-analysis of the proportion of patients with an Hb level ≥ 120 g/L.

Fig. 4. Forest plot for the meta-analysis of transferrin saturation (%).

Fig. 5. Forest plot for the meta-analysis of the FACIT-fatigue score.

(RR = 18.55; 95% CI = 8.66–39.72; $p < 0.00001$), with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $p = 0.37$) (Fig. 3).

Sensitivity Analysis

Low or even no heterogeneity is observed among the included studies for the proportion of patients with a ≥ 20 g/L Hb increase and an Hb level ≥ 120 g/L, and thus we do not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

Secondary Outcomes

Compared to the control group for iron deficiency anemia, ferumoxytol is able to substantially increase transferrin saturation (MD = 11.08; 95% CI = 9.86–12.31; $p < 0.00001$; Fig. 4) and FACIT-fatigue score (MD = 4.60; 95% CI = 3.21–6.00; $p < 0.00001$; Fig. 5), but shows no significant influence on adverse events (RR = 1.33; 95% CI = 0.84–2.10; $p = 0.22$; Fig. 6), serious adverse events (RR = 1.22; 95% CI = 0.74–2.02; $p = 0.44$; Fig. 7), and death (RR = 0.32; 95% CI = 0.05–1.95; $p = 0.22$; Fig. 8).

Fig. 6. Forest plot for the meta-analysis of adverse events.

Fig. 7. Forest plot for the meta-analysis of serious adverse events.

Fig. 8. Forest plot for the meta-analysis of death.

Discussion

Oral iron supplementation typically takes at least 2–3 weeks to increase the Hb concentrations and up to 2 months to achieve normal values. At least 6 months of treatment is needed to replenish iron stores completely [10, 16]. Intravenous iron may be the preferred treatment for many patients with iron deficiency anemia [30, 31]. Recent evidence-based international guidelines have rec-

ommended intravenous iron as the more effective and better tolerated method than oral iron [32]. The efficacy of intravenous iron supplementation in the treatment of iron deficiency anemia has been proven in patients with chronic kidney disease, abnormal uterine bleeding, pregnancy, postpartum anemia, cancer, and gastrointestinal disorders [22, 33–35]. Our meta-analysis suggests that intravenous ferumoxytol is able to substantially improve the proportion of patients with a ≥ 20 g/L Hb increase and

an Hb level ≥ 120 g/L, transferrin saturation, and FACIT-fatigue score in patients with iron deficiency anemia.

Ferumoxytol is the intravenous iron that has been investigated in the treatment of patients with iron deficiency anemia, and the increase in Hb after ferumoxytol treatment tends to be higher than when using other intravenous products [22]. For example, a single-arm study has reported that 4 weeks of treatment with low-molecular-weight iron dextran for patients with inflammatory bowel disease results in a mean Hb increase of 17 g/L [36]. The increases in Hb after ferumoxytol treatment needs the duration of 3–8 days compared with the treatment duration of 4–8 weeks for low-molecular-weight iron dextran [22].

Adverse events mainly include abdominal pain, diarrhea, nausea, headache, cough, dizziness, hypokalemia, leukopenia, neutropenia, vomiting, back pain, and constipation. Serious adverse events are hypersensitivity and anaphylactic reaction, death, life-threatening event, hospitalization, persistent or significant disability. The rates of adverse events (e.g., hypotension and hypersensitivity reactions) for ferumoxytol in patients with iron deficiency anemia are similar to those in the overall iron deficiency anemia study population [24]. Notably, the rates of serious adverse events are found to be low after ferumoxytol treatment for iron deficiency anemia, and ferumoxytol treatment is well tolerated in patients with gastrointestinal disorders similarly to the overall population of patients [6, 22]. Serious adverse events are similar be-

tween the ferumoxytol- and placebo-treated groups based on the results of our meta-analysis.

This meta-analysis has several potential limitations. Firstly, our analysis is based on only 4 RCTs and 1 of them has a relatively small sample size ($n < 100$). The number of patients in each RCT has a huge discrepancy. More RCTs with large samples should be conducted to confirm this issue. Next, iron deficiency anemia is caused by different diseases, which may have an influence on the pooling results. There is a lack of an active comparator other than placebo which may be a possible weakness in terms of efficacy assessment. Finally, some unpublished and missing data may lead to some bias.

Conclusions

Ferumoxytol is effective and safe to treat iron deficiency anemia and should be recommended in clinical work.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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