Safety and efficacy of a single total dose infusion (1020 mg) of ferumoxytol

Harris Khan, Paige May, Elim Kuo, Preetika Pai, Katherine Boles, Ashley McGee, Tanaka Dang and Jessica Schmit

Abstract
Purpose: Iron deficiency anemia (IDA) is the most common type of anemia. A single dose infusion of intravenous (IV) iron is a convenient treatment option. Ferumoxytol is an IV formulation of iron that is typically given in two doses of 510 mg each. Utilizing a single dose of 1020 mg over 15 min has previously been described as safe and effective. In July 2018, we began to administer a single 1020 mg dose of ferumoxytol to patients needing IV iron replacement at the North Florida/South Georgia Veterans Health System. To evaluate the impact of this change, a utilization review was conducted.

Methods: Outcomes of all patients who received ferumoxytol injections in the 6 months prior to and after the dosing strategy change were analyzed. A total of 140 patients, who received 270 separate IV ferumoxytol infusions, were included in the analysis.

Results: No significant difference in safety was observed, with one infusion reaction occurring in each group (p = 1.00). Efficacy also appeared equivalent with no significant difference between the change in hemoglobin for those who received a single 1020 mg dose versus those who received two 510 mg doses (p = 0.764). As expected, those who received a single total dose infusion of 1020 mg had less clinic utilization (p < 0.0001).

Conclusion: In summary, ferumoxytol administered as a 1020 mg single dose infusion was more convenient and should be considered a safe and effective treatment option for IDA.

Keywords: iron, iron compounds, iron-deficiency anemia, ferumoxytol

Introduction
Iron deficiency anemia (IDA) is the world’s most common type of anemia, comprising 50% of cases of anemia.1 In developed nations, iron deficiency is often secondary to chronic blood loss. Important less common causes of IDA include decreased iron absorption, usually secondary to celiac disease, proton pump inhibitors, atrophic gastritis, *Helicobacter pylori* infection or bariatric surgery.2 Iron restricted erythropoiesis (anemia of chronic disease) is seen with many conditions including chronic renal failure, chronic heart failure, malignancies, infections, and autoimmune diseases. Although patients are not total body iron depleted, poor iron utilization in this state leads to a functional iron deficiency.3 Treatment of iron deficiency involves both identifying and addressing the cause of iron deficiency, as well as replacing iron. There is a variety of intravenous (IV) and oral iron replacement formulations. Oral iron is widely available and relatively affordable; however, it is associated with a variety of gastrointestinal side effects, which may lead to poor adherence.4 IV iron does not cause such effects and is more effective in patients with malabsorption syndromes or gastric surgery. It also allows for the full replacement of iron stores in a short amount of time. However, there is a risk for adverse events, including hypersensitivity reactions and in very rare cases, anaphylactic shock.4 The cost of the drugs and need to obtain IV iron in an infusion clinic may pose an additional disadvantage for some patients.
There are multiple different IV iron formulations, which come in the form of iron-carbohydrate complexes or colloids. The general structure consists of a spheroidal particle with iron at its center, surrounded by a carbohydrate shell which serves to stabilize the molecule and slow the release of free iron. The choice of IV iron formulation is highly individualized and dependent upon product factors (i.e. infusion reaction rate and dosing frequency), patient factors (i.e. coexisting conditions and allergy history), formulary restrictions, and prescriber preference. Table 1 outlines the various available formulations of IV iron. Iron dextran was one of the earliest studied formulations. Currently, only low molecular weight iron dextran is used, as high molecular weight iron dextran has been associated with an increased number of rare but serious allergic reactions. Ferric gluconate and iron sucrose both have excellent safety profiles and are frequently used. Iron sucrose is, in fact, the most widely used formulation in the world. However, these two formulations consist of a smaller carbohydrate core that binds iron less tightly than dextran, resulting in significantly increased rates of free iron release. This limits the amount of iron that can be given as a single dose and thus requires multiple administrations to deliver the complete iron replacement dose. Other formulations include ferric carboxymaltose (FCM), which has been shown to be beneficial in the heart failure population, and ferric derisomaltose (formerly iron isomalto-side), both of which are composed of iron tightly bound to a carbohydrate moiety, which decreases the risk of labile iron toxicity, enabling them to be administered as a large one-time dose.

Ferumoxytol is a superparamagnetic iron oxide nanoparticle with a low molecular weight semisynthetic carbohydrate coating. It was originally developed as a contrast agent for magnetic resonance imaging (MRI) before it was recognized as an effective iron replacement strategy. Clinicians should be aware of ferumoxytol’s properties as an MRI contrast agent, as the radiographic findings may appear contrast enhanced for the first 3 months after infusion. In addition, the iron particle can mimic iron overload states such as hemochromatosis. It is otherwise an attractive option due to its quick administration time and low incidence of hypersensitivity reactions.

Ferumoxytol is typically given in two doses of 510 mg each. The 1020 mg dosing strategy was first described by Auerbach et al. in a single arm study of 60 patients treated with a single dose of 1020 mg of IV ferumoxytol and followed prospectively for safety and efficacy. In 2019, Karki and Auerbach published their experience using this replacement strategy on 176 consecutive patients, finding it to be both safe and effective. This dose has been described in the literature as the maximum safe dose. A one-time dose is attractive due to the convenience of less travel and infusion visits for patients and more efficient utilization of infusion room space and staff. In July 2018, we began to administer a single 1020 mg dose of ferumoxytol as our standard IV iron replacement strategy at the North Florida/South Georgia Veterans Health System in Gainesville, Florida, USA. A retrospective chart review was conducted to evaluate the effects of this change in terms of safety, efficacy, and clinic utilization.

**Methods**

Data were collected on patients who received ferumoxytol between 1 February 2018 and 31 January 2019 at the North Florida/South Georgia Veterans Health System to capture approximately 6 months of data prior to, and after, a hospital-wide transition from two doses of 510 mg to a single dose of 1020 mg of IV ferumoxytol as the standard iron replacement strategy at our institution. Our primary goal was to assess safety, efficacy and clinic utilization when using a total dose infusion of 1020 mg of ferumoxytol. Prior to commencing, this project was determined to be quality assurance, as defined by the US Code of Federal Regulations. Thus, it did not undergo institutional review board review or require informed patient consent. The single total dose infusion was administered over 15 min followed by nursing observation for 15–30 min.

Patients were included if they received a dose of IV ferumoxytol during the study period. Patients were excluded if they had received IV iron in the 3 months prior to the study period. Patient demographics, number and dose of iron infusions received, observed adverse reactions, and treatment response were recorded. We separated our analysis into two groups, one for safety and one for efficacy. All patients and doses of IV ferumoxytol were included in an analysis of safety. Patients were excluded from the efficacy analysis if they had received both dosing strategies (1020 mg and
| IV iron product                                | Brand name            | Standard label maximum single dose | Infusion time | Recommended doses | Risk and incidence of HSRs | Average wholesale price | Miscellaneous |
|------------------------------------------------|-----------------------|-----------------------------------|---------------|------------------|-----------------------------|--------------------------|---------------------|
| Low molecular weight iron dextran             | Cosmofer® INFeD®      | 1000 mg                           | 4–6 h; 1-h infusion has also been described¹⁰ | Multiple doses of 100 mg or single dose of 1000 mg | Highest risk¹¹           | $0.35/mg            | Test dose required with 1-h observation period |
| Ferric gluconate                              | Ferrlecit®            | 125 mg                            | 60 min        | Multiple doses   | Low risk                   | $1.64/mg               |                     |
| Iron sucrose                                  | Venofer®              | 500 mg                            | 3.5–5 h       | Multiple doses   | Low risk                   | $0.60/mg               |                     |
| Ferumoxytol                                    | Feraheme® Rienso®     | 510 mg                            | 15 min        | Two doses given 3–8 days apart | Low risk                   | $2.50/mg               | MRI scans may appear contrast enhanced for up to 3 months following use¹⁸ |
| Ferric carboxymaltose (FCM)                   | Ferinject® Injectafer® | 750 mg for patients over 50 kg; 15 mg/kg for patients <50 kg | 15 min        | Two doses given 7 or more days apart | Low risk                   | $1.82/mg               | Hypophosphatemia is seen in 50% of patients and can persist five weeks or more²⁰ |
| Ferric derisomaltose (formerly iron isomaltoside) | Monoferric® Monofer® | 20 mg/kg, not to exceed 1500 mg   | 15–30 min     | Single dose      | Low to intermediate risk   | Not available            | Associated with fetal bradycardia following maternal administration²¹ |

HSR, hypersensitivity reaction; IV, intravenous.
510 mg) during the study period. Pre-treatment laboratory values (baseline iron saturation, hemoglobin, and ferritin) were included irrespective of the duration of time that had elapsed prior to the first infusion of IV iron. Response was assessed by recording post-treatment laboratory studies drawn within 12 weeks from infusion. If more than one value was available, the highest number was recorded for each group.

The number of visits, baseline and change in hemoglobin, ferritin and iron saturation were compared using paired t-tests. The rate of infusion reactions was compared using Fisher’s exact test.

Results

A total of 140 patients met the criteria for analysis. Of these, 119 were included in the efficacy analysis: 59 patients who received only 510 mg doses and 60 patients who received only the 1020 mg dose. Baseline characteristics were similar between the two groups and are summarized in Table 2. The other 21 patients received both 510 mg and 1020 mg doses during the study period, and were included in the safety analysis, but not efficacy. A total of 270 separate infusions of IV iron were given during the study period (96 infusions of 1020 mg and 174 infusions of 510 mg) and were included in the safety analysis.

Efficacy was similar between the two dosing strategies as shown in Table 3. The mean increase in hemoglobin concentration was 1.96 g/dL for those who received two doses of 510 mg and 2.00 g/dL for those who received one dose of 1020 mg (p = 0.726). The mean increase in ferritin was also similar in the two groups, 114 ng/mL and 120 ng/mL, respectively (p = 0.820). The mean rise in iron saturation was 13.6% and 14.3%, respectively (p = 0.781). All response assessments were done within 12 weeks; two patients (one in each group) did not have a starting ferritin.

Administering the 1020 mg dose significantly reduced the number of infusion room visits required, with an average of two visits for those receiving 510 mg and one visit for those receiving 1020 mg (p < 0.0001).

When evaluating the infusion reaction rate, all doses of iron during the study period were included in the safety analysis (n = 270); 174 individual infusions of the 510 mg dose of IV ferumoxytol and 96 infusions of the 1020 mg dose of IV ferumoxytol were given during the study period. The rate of infusion reactions was not increased, with only one reaction occurring in each group: pruritis (0.57%) and nausea with vomiting (1.04%), respectively (p = 1.00). Both reactions were mild to moderate in nature and were managed with treatment interruption in both cases, and IV steroids in the case of pruritus. All were discharged from the infusion clinic on the same day.

Discussion

The single total dose infusion of 1020 mg of IV ferumoxytol led to a decrease in the number of infusion room visits, without significantly increasing the rate of infusion reactions or compromising efficacy, as compared to the traditional dosing of two infusions of 510 mg of ferumoxytol administered 1 to 2 weeks apart. Single dose infusion is an attractive option as it is more convenient and reduces the number of visits to the infusion room.

Many patients who receive IV iron for IDA require repeated administration due to either ongoing blood loss or chronic poor absorption. Although the risk of infusion reactions remains a concern, the risk of serious adverse effects remains very low with newer IV iron formulations. The safety and efficacy among the various IV iron formulations, including low molecular weight iron dextran, ferumoxytol, ferric derisomaltose, and FCM, has been found to be comparable when administered as single infusions among a variety of settings. Recently, ferumoxytol administered as two doses of 510 mg demonstrated non-inferiority to FCM in terms of safety and efficacy in a randomized double-blind comparison. The use of IV iron may prevent the requirement for red blood cell transfusions, which is associated with a high side effect profile.

The present report is the first retrospective review of its kind directly comparing the two dosing strategies of IV ferumoxytol. This review substantiates prior literature published by Auerbach et al. demonstrating the safety and efficacy of a single 1020 mg dose. In the Auerbach study, the adverse event rate was high at 43.3%, although all reactions were mild and transient. In the present...
Table 2. Baseline characteristics.

| Variable                        | 510 mg (n = 59) | 1020 mg (n = 60) | Significance (p-value) |
|---------------------------------|-----------------|------------------|------------------------|
| Age (years)                     |                 |                  |                        |
| Mean                            | 67              | 64               | *p = 0.265*            |
| Range                           | [38–92]         | [25–94]          |                        |
| Gender [no. (%)]                |                 |                  |                        |
| Male                            | 43 [72.9]       | 46 [76.7]        | *p = 0.638*            |
| Female                          | 16 [27.1]       | 14 [23.3]        |                        |
| Cause of iron deficiency [no. (%)] |               |                  |                        |
| Gastrointestinal bleeding       | 37 [62.7]       | 33 [55]          | *p = 0.192*            |
| Heavy menses                    | 6 [10.2]        | 11 [18.3]        |                        |
| Poor absorptive state           | 0 [0]           | 2 [3.3]          |                        |
| Unknown                         | 16 [27.1]       | 14 [23.3]        |                        |
| Baseline hemoglobin [g/dL]      |                 |                  |                        |
| Mean                            | 9.8             | 9.7              | *p = 0.726*            |
| Range                           | [6.7–14.6]      | [6.7–13.3]       |                        |
| Distribution [no. (%)]          |                 |                  |                        |
| <7.0                            | 3 [5.1]         | 3 [5.0]          |                        |
| 7.1–9.0                         | 15 [25.4]       | 18 [30.0]        |                        |
| 9.1–11.0                        | 30 [50.8]       | 29 [48.3]        |                        |
| >11.0                           | 11 [18.7]       | 10 [16.7]        |                        |
| Baseline ferritin (ng/mL)       |                 |                  |                        |
| Mean                            | 38.2            | 26.2             | *p = 0.292*            |
| Range                           | [3–415]         | [4–417]          |                        |
| Distribution [no. (%)]          |                 |                  |                        |
| <30                             | 40 [67.8]       | 45 [75.0]        |                        |
| 30–100                          | 14 [23.7]       | 13 [21.6]        |                        |
| 100–200                         | 2 [3.4]         | 0 [0]            |                        |
| >200                            | 2 [3.4]         | 1 [1.7]          |                        |
| Not checked                     | 1 [1.7]         | 1 [1.7]          |                        |
| Baseline iron saturation (%)    |                 |                  |                        |
| Mean                            | 9.0             | 11.4             | *p = 0.216*            |
| Range                           | [3–28]          | [3–78]           |                        |
| Distribution [no. (%)]          |                 |                  |                        |
| <10                             | 37 [62.7]       | 39 [65.0]        |                        |
| 10–20                           | 20 [33.9]       | 16 [26.7]        |                        |
| 20–30                           | 2 [3.4]         | 3 [5.0]          |                        |
| >30                             | 0 [0]           | 2 [3.3]          |                        |
review, the adverse event rate was very low (0.57% and 1.04% in 510 mg and 1020 mg arms, respectively), with only one reaction in each arm. Both events occurred during the first couple of minutes of infusion and were treated with interruption of the infusion and administration of rescue medications. Both would be classified as grade II using the Ring and Messner hypersensitivity reaction grading scale. As per the revised Sampson et al. criteria of anaphylaxis, neither patient developed anaphylaxis. Rampton et al. have published an excellent clinical review on the management of iron hypersensitivity reactions. Our review did not follow patients after discharge from the clinic and this may have contributed to the relatively low number of adverse events in our study compared to that of Auerbach et al. However, the causality of such subjective adverse events happening up to 8 weeks post-discharge in Auerbach et al. may be difficult to establish and their significance may have been overstated. In the follow-up study published in 2019, 7.4% of patients reported minor reactions.

A potential barrier to other institutions implementing a total dose infusion of ferumoxytol is the variability of medical insurance coverage of this off-label dosage. However, many major medical insurance carriers are now covering the single total dose. As this review was conducted within the Veterans Health Administration, providers did not need to work with private medical insurances to gain approval for payment.

This review has several limitations. As a quality assurance project, our goal was to assess safety, efficacy, and efficiency of this dosing change. Therefore, we did not impose strict inclusion criteria to ensure uniformity of the population. As noted in the table of efficacy (Table 3), some of our population had a decrease in their measured iron stores after IV iron. This may have happened due to the study design. We included any baseline hemoglobin, ferritin and percentage saturation, regardless of the time that lapsed prior to the actual IV infusion. We also did not impose strict post-treatment inclusion criteria and any laboratory data collected within 12 weeks were included as response assessment. There was large heterogeneity in patients’ pre-treatment and post-treatment laboratory measurements.

Our review was not targeted to specific populations, such as those with chronic kidney disease. Furthermore, we did not define iron deficiency as part of our inclusion criteria. Most of our patients met laboratory criteria for iron deficiency; however, some did not and likely did not actually need or benefit from an IV iron infusion. As practice patterns vary widely in the real-world setting, these findings are likely to be more representative of actual clinical practice data. We also did not attempt to explore factors that may have influenced results, such as the number of patients who received blood transfusions or who were receiving oral iron during the study period.

### Table 3. Comparison of efficacy.

| Response assessment | 510 mg (n = 59) | 1020 mg (n = 60) | Significance (p-value) |
|--------------------|----------------|-----------------|-----------------------|
| Change in hemoglobin (g/dL) | | | p = 0.764 |
| Mean | 2.0 | 2.0 | |
| Range | (-0.8–5.9) | (-1.0–5.7) | |
| Change in ferritin (ng/mL) | | | p = 0.820 |
| Mean | 114 | 120 | |
| Range | (-92–496) | (-8–1012) | |
| Change in iron saturation (%) | | | p = 0.781 |
| Mean | 13.6 | 14.3 | |
| Range | (-14–47) | (-49–173) | |

*Measured within 12 weeks of infusion.*
We performed our data analysis after the intervention had been performed, which may have led to bias. Our small sample size may have led to an inability to detect small differences in efficacy between the two dosing strategies. We did not detect any serious infusion reactions during manual chart review. Mild reactions were recorded when documented in the medical record. The actual rate of mild reactions may have been higher but were missed because of the study design. Because serious infusion reactions are rare, a much larger sample size would be needed to detect significant differences between the two groups in terms of safety.

Implementation of a single total dose infusion of 1020 mg of ferumoxytol was safe and effective. Administering ferumoxytol as a one-time dose reduced the number of infusion room visits without increasing infusion reactions or compromising efficacy. Ultimately, this strategy of implementing a one-time outpatient total dose infusion of 1020 mg of ferumoxytol could be considered at other institutions to improve infusion room access, patient convenience, and reduce costs.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical statement
Our study did not require ethical board approval because this was reviewed and approved as a quality improvement study.

ORCID iD
Harris Khan https://orcid.org/0000-0003-4055-4019

References
1. United Nations Children’s Fund (UNICEF), United Nations University (UNU), World Health Organization (WHO). Iron deficiency anemia: assessment, prevention, and control: a guide for programme managers. Geneva: WHO; 2001, pp. 47–62.
2. Camaschella C. Iron-deficiency anemia. N Engl J Med 2015; 372: 1832–1843.
3. Cullis J. Anaemia of chronic disease. Clin Med (Lond) 2013; 13: 193–196.
4. Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 2015; 90: 12–23.
5. Auerbach M and Macdougall I. The available intravenous iron formulations: history, efficacy, and toxicology. Hemodial Int 2017; 21: S83–S92.
6. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; 361: 2436–2448.
7. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2015; 36: 657–668.
8. Bhandari S, Kalra PA, Kothari J, et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients. Nephrol Dial Transplant 2015; 30: 1577–1589.
9. McKesson Wholesale Pharmaceuticals Ltd. McKesson Wholesale Pharmaceuticals Ltd. https://connect.mckesson.com/portal/site/smo/Home?link=tn (accessed 28 July 2020).
10. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117: 391–397.
11. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015; 314: 2062–2068.
12. Auerbach M, Pappadakis JA, Bahrain H, et al. Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. Am J Hematol 2011; 86: 860–862.
13. Fishbane S, Ungureanu VD, Maesaka JK, et al. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 1996; 28: 529–534.
14. Michael B, Coyne DW, Fishbane S, et al. Sodium ferric gluconate complex in hemodialysis patients:
adverse reactions compared to placebo and iron dextran. *Kidney Int* 2002; 61: 1830–1839.

15. Hetzel D, Strauss W, Bernard K, et al. A phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. *Am J Hematol* 2014; 89: 646–650.

16. Auerbach M, Henry D, Derman RJ, et al. A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. *Am J Hematol* 2019; 94: 1007–1014.

17. Adkinson NF, Strauss WE, Macdougall IC, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. *Am J Hematol* 2018; 93: 683–690.

18. Schieda N. Parenteral ferumoxytol interaction with magnetic resonance imaging: a case report, review of the literature and advisory warning. *Insights Imaging* 2013; 4: 509–512.

19. Mulder MB, van den Hock HL, Birnie E, et al. Comparison of hypersensitivity reactions of intravenous iron: iron isomaltoside-1000 (Monofer®) versus ferric carboxy-maltose (Ferinject®). A single center, cohort study. *Br J Clin Pharmacol* 2019; 85: 385–392.

20. Wolf M, Chertow GM, Macdougall IC, et al. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight* 2018; 3: e124486.

21. Woodward T, Kay T and Rucklidge M. Fetal bradycardia following maternal administration of low-molecular-weight intravenous iron. *Int J Obstet Anesth* 2015; 24: 196–197.

22. McCullough BJ, Kolokythas O, Maki JH, et al. Ferumoxytol in clinical practice: implications for MRI. *J Magn Reson Imaging* 2013; 37: 1476–1479.

23. Feraheme [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc., 2014.

24. Toth GB, Varalayay CG, Horvath A, et al. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. *Kidney Int* 2017; 92: 47–66.

25. Auerbach M, Strauss W, Auerbach S, et al. Safety and efficacy of total dose infusion of 1,020 mg of ferumoxytol administered over 15 min. *Am J Hematol* 2013; 88: 944–947.

26. Karli NR and Auerbach M. Single total dose infusion of ferumoxytol (1020mg in 30 minutes) is an improved method of administration of intravenous iron. *Am J Hematol* 2019; 94: E229–E231.

27. Auerbach M and Adamson JW. How we diagnose and treat iron deficiency anemia. *Am J Hematol* 2016; 91: 31–38.

28. Schrier SL. Treatment of the adult with iron deficiency anemia. In: Post TW (ed.) *UpToDate*. Waltham, MA: UpToDate, 2020.

29. 45 CRF 46.102: Protection of human subjects. Hhs.gov. https://ori.hhs.gov/content/chapter-3-The-Protection-of-Human-Subjects-45-crf-46102-protection-human-subjects (accessed 8 February 2021).

30. Moniem K and Bhandari S. Tolerability and efficacy of parenteral iron therapy in hemodialysis patients, a comparison of preparations. *Transfus Alternat Transfus Med* 2007; 9: 37–42.

31. Michael A, William ES, Iain CM, et al. Randomized, double-blind trial of ferumoxytol compared to ferric carboxymaltose for treatment of iron deficiency anemia: safety and efficacy. *Blood* 2017; 130 (Suppl. 1): 3500.

32. Litton E, Xiao J and Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. *BMJ* 2013; 347: f4822.

33. Ring J and Messner K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 309: 466–469.

34. Rampton D, Folksersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica* 2014; 99: 1671–1676.