



Frequency and Associated Costs of Anaphylaxis- and Hypersensitivity-Related Adverse Events for Intravenous Iron Products in the USA: An Analysis Using the US Food and Drug Administration Adverse Event Reporting System

Henry Trumbo¹ · Karolina Kaluza² · Syed Numan² · Lawrence T. Goodnough³

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Abstract

Introduction and Objective Intravenous iron preparations rapidly correct iron deficiency anemia, with the notable drug class effect of rare, yet potentially life-threatening, administration-related hypersensitivity or anaphylactic reactions. The objective of this comparative study was to assess adverse events associated with four intravenous iron preparations and estimated medical costs, in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods Cases of hypersensitivity reactions and anaphylaxis/anaphylactic shock associated with iron dextran, iron sucrose, ferumoxytol, and ferric carboxymaltose, spontaneously reported to FAERS (1 January, 2014 to 31 December, 2019), were extracted. The reporting odds ratio lower bound 90% confidence interval (ROR05) > 1 and cases ≥ 5 defined a likely signal for a drug–adverse event association. Adverse event-associated medical costs were estimated using Agency for Healthcare Research and Quality/Healthcare Cost and Utilization Project 2016 data.

Results For hypersensitivity reactions, ferumoxytol and iron dextran had the highest ROR05 values (5.00 and 4.35, respectively) and greatest proportions of associated deaths (7.1% and 5.3%), followed by iron sucrose (ROR05 3.94, deaths 2.4%), and ferric carboxymaltose (ROR05 3.03, deaths 0.2%). For anaphylaxis/anaphylactic shock, ROR05 for cases/deaths were: 39.32/13.4%, ferumoxytol; 37.80/4.5%, iron dextran; 17.60/4.7%, iron sucrose; and 8.77/no deaths, ferric carboxymaltose. Downstream medical costs per adverse event were highest with iron dextran (US\$8615) and ferumoxytol (US\$8164), followed by iron sucrose (US\$4212), and ferric carboxymaltose (US\$1832).

Conclusions Reporting rates of hypersensitivity and anaphylaxis with intravenous iron preparations were highest with ferumoxytol and lowest with ferric carboxymaltose in the US FAERS database. Adverse event-related medical costs were highest for iron dextran and ferumoxytol, and lowest for ferric carboxymaltose.

1 Introduction

Iron deficiency is the most frequent cause of anemia, which affects 32.9% of the global population [1], and of all nutrient deficiencies, it is the only one that is also commonly

detected in industrialized countries [2]. Both iron deficiency and anemia have substantial socioeconomic consequences in terms of reductions in school performance and work productivity [2]. There are numerous causes of iron deficiency anemia [3], but usually the first step in managing iron deficiency is to begin with oral iron supplementation [3–5] because an improved diet alone may not address iron repletion needs [5]. Intravenous (IV) iron preparations are reserved for the treatment of patients who cannot tolerate oral iron, have not responded well to oral iron, or for those patients who would benefit from rapid restoration of iron stores [3–5].

The first IV iron preparation to be used was ferric hydroxide, introduced in the early 1930s, but it was found to be associated with serious toxic reactions related to the immediate systemic release of iron [6]. Consequently, new iron preparations were developed utilizing a carbohydrate shell

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✉ Henry Trumbo
htrumbo@stmaryhealthcare.org

¹ Pharmacy Department, St. Mary Medical Center, 1201 Langhorne-Newtown Road, Langhorne, PA 19047, USA

² American Regent, Norristown, PA, USA

³ Stanford University, Stanford, CA, USA

Key Points

Iron deficiency anemia can be rapidly corrected and managed with intravenous iron products; however, rare hypersensitivity or anaphylactic reactions associated with their administration have occurred.

Reporting rates of hypersensitivity and anaphylactic reactions with four intravenous iron preparations (iron dextran, iron sucrose, ferumoxytol, and ferric carboxymaltose) were assessed based on the US Food and Drug Administration Adverse Event Reporting System database.

There were differential reporting rates of hypersensitivity and anaphylactic reactions for intravenous iron products, with ferric carboxymaltose exhibiting the lowest reporting rate and the lowest downstream medical costs per adverse event.

enclosing an iron core, thereby preventing the immediate release of iron and improving tolerability [6, 7]. The initial iron saccharide preparations were replaced with high-molecular-weight iron dextran preparations in the 1950s. These latter preparations became the mainstay of IV iron therapy; however, they were associated with rare but serious cases of acute hypersensitivity reactions or anaphylaxis [8]. Since the 1970s, a number of additional iron preparations have become available to replace high-density molecular-weight iron dextran: first low-molecular-weight iron dextran (US approval April 1974), ferric gluconate (US approval February 1999), and iron sucrose (US approval June 2000), and more recently ferumoxytol (US approval June 2009), ferric carboxymaltose (US approval July 2013), and iron isomaltoside (US approval January 2020) [6, 7].

All IV iron preparations share a common structure of an Fe^{3+} hydroxide particle containing a polynuclear core surrounded by a carbohydrate shell in a colloidal solution [7]. However, the chemistry of the carbohydrate moiety forming the shell and the type and strength of the bonds with the iron core vary, resulting in differences of iron stability within the carbohydrate complex. The lower the stability of the complexes, the faster the systemic release of ferric iron and, in general, the greater the risk of infusion reactions, including serious hypersensitivity and anaphylactoid reactions. The three newest IV iron preparations (ferumoxytol, iron isomaltoside, and ferric carboxymaltose) have more stable carbohydrate shells than the earlier preparations [7]. It is important to determine whether this improved stability has correspondingly reduced the risk of hypersensitivity and anaphylactoid reactions. Although all IV iron preparations are associated with the class risk of serious hypersensitivity

reactions and anaphylaxis [4] and black-box warnings for these events have been added to the prescribing information for some IV iron preparations [9, 10], the risk is rare [7, 8]. Given the rarity of these serious reactions, randomized controlled trial evidence and associated meta-analyses have been unable to demonstrate meaningful differences between IV iron preparations [11–13]. Large observational claims database retrospective analyses have suggested these reactions may be more frequent with iron dextran vs newer preparations [4] and with ferumoxytol vs iron sucrose (see Supplementary Table S5 in Wetmore et al. [14]), and pharmacovigilance spontaneous reporting database analyses have suggested higher reporting rates with iron dextran, ferumoxytol, and iron isomaltoside than ferric gluconate or ferric carboxymaltose [8, 15–18]. However, methodological concerns [19–23] and a paucity of longer term data on newer IV iron preparations in many of these publications limit the conclusions that can be reached. Thus, up-to-date analyses are required to further explore signals for potential IV iron–adverse event (AE) associations using established methodologies for analysis of pharmacovigilance spontaneous reporting databases [24, 25].

Here, we analyzed real-world AEs associated with IV iron products spontaneously reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database [26, 27] using established methodologies [28–31]. Estimated consequent medical costs associated with these AEs were calculated using 2016 Agency for Healthcare Research and Quality (AHRQ)/Healthcare Cost and Utilization Project (HCUP) data [32, 33]. For all analyses, we evaluated IV iron preparations currently approved in the USA for the treatment of iron deficiency anemia, namely iron dextran, iron sucrose, ferumoxytol, and ferric carboxymaltose. The approval date of iron isomaltoside in the USA (January 2020) was too recent for this product to be meaningfully included in the current analysis.

2 Methods

2.1 FAERS Analysis

2.1.1 Data Source, Extraction, and Processing

The FAERS is a nationally centralized and computerized information database broadly used by the FDA and other pharmacovigilance experts for post-marketing drug safety surveillance. The FAERS data are made publicly available as a quarterly download on the FDA's website (FDA 2019) [27], but to obtain accurate insight from the database, extensive data cleansing and normalization was applied. Advera's Evidex[®] platform [28, 30], using RxFilter[®] data optimization technology and based upon established algorithms [29],

was utilized to create a clean, drug-mapped, de-duplicated version of the FAERS data for analysis.

Post-marketing case reports of prespecified AEs associated with branded and generic formulations of four IV iron products: iron dextran, iron sucrose, ferumoxytol, and ferric carboxymaltose (a full list of included products is provided in Table S1 of the Electronic Supplementary Material [ESM]) submitted to FAERS between 1 January, 2014 and 31 December, 2019 were extracted. The AEs of interest for these analyses, defined according to the Medical Dictionary for Regulatory Activities (MedDRA[®]) version 22.0 preferred terms (PTs) [34] and Standardized Medical Queries (SMQs) [35], were hypersensitivity reaction individual PTs and the hypersensitivity SMQ and anaphylaxis/anaphylactic shock individual PTs and the anaphylactic reaction SMQ. For SMQ searches, “narrow” scope groupings of PT terms were used. Data validation steps were run to verify that all case reports had completed key identification fields, including the patient identifier, case identifier (each patient could have multiple AE case reports), drug sequence identification, and MedDRA[®] AE terms [29]. Case reports containing incorrectly completed or missing key identification fields were discarded [29]. The proportion of reports with missing key identification fields was calculated to assess the frequency of discarded reports. Among retained reports, the proportion of missing data for the outcomes field (which contains hospitalization and death information), and for age and sex information, were also calculated. Drug mapping steps were then undertaken before duplicate case reports were removed [29].

Primary suspect cases were defined as case reports where the reporter designated a particular drug as the most likely cause of the given side effect; if the patient was taking other drugs at the time of the AE, those drugs were listed as “concomitant” or “secondary” causes. Total suspect cases were defined as all case reports where the specified drug was mentioned in the case report, including: primary suspect, secondary suspect, concomitant, interacting, or not specified (the “suspect” field in FAERS was not filled in).

2.1.2 Data Analysis

Overall number of case reports and primary suspect case counts associated with AEs of interest (hypersensitivity reactions and anaphylaxis/anaphylactic shock) and the proportions of cases associated with hospitalization and/or death related to these AEs were calculated, and disproportionality analyses were conducted for the US region. The reporting odds ratio (ROR) [36] was used to identify the strength of association between each iron preparation and AE of interest and was chosen over the proportional reporting ratio because the latter measure produces biased estimates of the rate or risk ratio whereas the ROR does not

[31]. The ROR is the pharmacovigilance equivalent of the odds ratio and is defined here as the odds for the AE of interest occurring among the group of case reports for patients receiving the specific IV iron preparation under investigation divided by the odds for the AE of interest occurring in the comparison group of case reports for patients receiving any other drug administered by any route, where the odds of the event is the probability that the event will occur divided by the probability that the event does not occur [37]. The limits of the 90% CI of ROR were obtained via an approximation of the normal distribution as described by Van Puijenbroek et al. [38]. Based on the ROR distribution, the lower bound (ROR05) of the CI was calculated, as it provided 95% certainty that the true mean of the population was at or above the number reported. There is no universally accepted benchmark regarding the numerical level/threshold at which disproportionality analysis signal detection algorithms identify adverse drug reactions [39, 40], thus we defined values of $ROR05 \geq 1$ and cases ≥ 5 as a signal of a likely drug–AE association. Our main analysis used primary suspect case counts, but we also performed a sensitivity analysis using total suspect case counts. In addition, we performed further analyses to support our primary analysis, notably stratified analyses by age (< 65 vs ≥ 65 years) and sex, and a calculation of the masking ratio for the ROR05 [41, 42]. A disproportionate signal for a given drug–event pair can be masked because of the presence of a disproportionate signal for another drug with the same event of interest in the same database [41]. According to Maignen et al., we calculated the masking ratio for the ROR05 (MRCI) by dividing the ROR05 using the comparison group for the ROR without all other IV iron preparations by the ROR05 calculated for the main analysis (i.e., using the comparison group for the ROR with all other IV iron preparations); an MRCI substantially > 1 indicates masking [42].

3 Costs Analysis

The methods of Hoffman et al. [43] were used to estimate direct downstream medical costs associated with hypersensitivity reactions and anaphylaxis/anaphylactic shock, and unfavorable patient outcomes for each IV iron preparation. The AE and patient outcome data obtained from FAERS case reports were mapped to AE-specific and associated outcome costs based on the most recently available national inpatient hospitalization and aggregate costs for specific diagnoses and procedures obtained from AHRQ/HCUP 2016 data [32, 33]. The cost of hospital death was based on the average cost of a hospital stay ending in death in 2007, as reported in the analyses of Zhao and Encinosa [44]. No discounting was performed and costs were not adjusted by year.

Data from HCUP were coded to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) using BioPortal [45], a repository of biomedical ontologies, and an ICD-10 mapping resource was used to assign ICD-10-CM codes to MedDRA® PTs (Table S2 of the ESM). Preferred Terms that could not be directly assigned by the use of BioPortal were manually mapped using the ICD-10-CM coding manual.

To determine medical cost estimates, the frequency of AEs resulting in hospitalization or death were multiplied by the average hospitalization costs and average cost of a hospital stay ending in death, respectively, for each iron preparation. All costs were inflation adjusted on a yearly basis using the medical care services component of the consumer price index (not seasonally adjusted) for each month of December obtained from the US Bureau of Labor Statistics [46]. These costs were aggregated to determine the total medical costs for each drug. Average costs per AE were calculated by dividing the total medical costs for each preparation by the total number of AEs with available cost mapping reported for each IV iron preparation. Average costs per patient for each preparation were calculated by dividing the total medical costs by the total number of patients receiving each IV iron preparation (the total number was estimated from IQVIA [Durham, NC, USA] IV Iron Landscape Claims Data 2019).

4 Results

4.1 AEs Reported for IV Iron Preparations

Of a total of 5,027,033 FAERS case reports during the period of study (1 January, 2014 to 31 December, 2019), 95 had missing MedDRA® AE terms, meaning that our primary suspect and total suspect case count analysis had a coverage of 99.998% of case reports for the overall ROR05 estimates. However, missing data were present to a much greater extent for the outcome field in FAERS (57.2%), meaning that percentages and ROR05 values for hospitalization and death were based upon a 42.8% coverage. For our stratified analyses, age was not specified in 47.2% of cases and sex was not specified in 11.1% of cases.

Primary suspect case counts and disproportionality associated with each reported AE of interest are summarized in Table 1 and Fig. 1. Each of the four iron preparations had an ROR05 for overall SMQ hypersensitivity reactions that was considered a signal of a likely drug–AE association. The ROR05 was highest for ferumoxytol, followed by iron dextran, iron sucrose, and ferric carboxymaltose (Table 1; Fig. 1). For primary suspect cases resulting in death associated with SMQ hypersensitivity reactions, ferumoxytol and iron sucrose had 14 and 5 deaths, respectively, and

had ROR05 values (18.53 and 3.77, respectively) that were considered signals for a likely drug–death association; ferric carboxymaltose had only one reported death (Table 1; Fig. 1). Although the ROR05 for death associated with SMQ hypersensitivity reactions indicated a signal for iron dextran (ROR05 8.01), the absolute number of cases ($n = 3$) fell below the signal detection threshold, likely owing to the low number of overall reports with iron dextran during the time-frame of the study. For primary suspect cases resulting in hospitalization associated with SMQ hypersensitivity reactions, ferric carboxymaltose had the lowest ROR05 value (ROR05 1.2 vs 5.98–9.81 for other IV iron preparations: Table 1; Fig. 1).

All IV iron preparations had an ROR05 for an overall SMQ anaphylactic reaction that was considered a signal of a likely drug–AE association. The ROR05 was highest for ferumoxytol, followed by iron dextran, iron sucrose, and ferric carboxymaltose (Table 1; Fig. 1). For primary suspect cases resulting in death associated with an SMQ anaphylactic reaction, no deaths were reported with ferric carboxymaltose, whereas ferumoxytol had nine deaths and the ROR05 (41.88) represented a signal for a likely drug–death association (Table 1; Fig. 1). Although ROR05 values for death associated with an SMQ anaphylactic reaction were elevated for iron dextran (5.20) and iron sucrose (3.85), the absolute number of cases ($n = 1$ and 2, respectively) fell below the signal detection threshold. For primary suspect cases resulting in hospitalization associated with an SMQ anaphylactic reaction, ferric carboxymaltose had the lowest ROR05 value (ROR05 1.79 vs 17.21–42.47 for other IV iron preparations: Table 1; Fig. 1).

Our sensitivity analysis using total suspect case counts showed very similar ROR05 patterns across the IV iron preparations to those using only primary suspect case counts (Table S3 of the ESM); and ROR05 values for the SMQ anaphylactic reaction, and associated deaths and hospitalizations were lowest with ferric carboxymaltose. The stratified analysis of primary suspect case counts by age showed ROR05 values (with at least five cases in each age group) indicating a likely drug–AE association for an SMQ anaphylactic reaction in both age groups, but ROR05 values were higher among patients aged ≥ 65 vs < 65 years across all IV iron preparations; ROR05 values were lowest with ferric carboxymaltose in both age groups (Table S4 of the ESM). ROR05 values for hospitalization due to SMQ hypersensitivity were higher among patients aged ≥ 65 vs < 65 years for iron dextran, iron sucrose, and ferumoxytol, and ROR05 values for hospitalization due to an SMQ anaphylactic reaction were higher among patients aged ≥ 65 vs < 65 years for iron sucrose and ferumoxytol. The stratified analysis of primary suspect case counts by sex showed that ROR05 values (with at least five cases in both male and female patients) for SMQ hypersensitivity or an SMQ anaphylactic reaction

Table 1 Primary suspect case counts and disproportionality associated with AEs of interest and death and hospitalizations associated with those AEs reported in the USA from 1 January, 2014 to 31 December, 2019

AE	Iron dextran			Iron sucrose			Ferumoxytol			Ferric carboxymaltose						
	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)
SMQ narrow grouping																
Hypersensitivity	57	4.35	3 (5.3)	19 (33.3)	212	3.94	5 (2.4)	46 (21.7)	196	5.00	14 (7.1)	50 (25.5)	401	3.03	1 (0.2)	25 (6.2)
Anaphylactic reaction	22	37.8	1 (4.5)	11 (50.0)	43	17.6	2 (4.7)	18 (41.9)	67	39.32	9 (13.4)	26 (38.8)	51	8.77	0 (0.0)	6 (11.8)
Individual preferred terms^a																
Anaphylactic reaction	17	42.88	1 (5.9)	7 (41.2)	31	18.95	2 (6.5)	15 (48.4)	60	54.61	8 (13.3)	25 (41.7)	43	11.44	0 (0.0)	4 (9.3)
Anaphylactic shock	5	42.13	0 (0.0)	4 (80.0)	6	12.17	0 (0.0)	2 (33.3)	4	8.95	0 (0.0)	2 (50.0)	3	1.93	0 (0.0)	2 (66.7)
Anaphylactoid reaction	0	-	0 (0.0)	0 (0.0)	4	36.1	0 (0.0)	1 (25.0)	3	30.56	0 (0.0)	0 (0.0)	5	20.79	0 (0.0)	0 (0.0)
Angioedema	4	7.25	0 (0.0)	1 (25.0)	6	2.87	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.08	0 (0.0)	0 (0.0)
Bronchospasm	0	-	0 (0.0)	0 (0.0)	2	2.97	0 (0.0)	0 (0.0)	7	23.23	0 (0.0)	1 (14.3)	1	0.39	0 (0.0)	0 (0.0)
Circulatory collapse	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	2.09	1 (100.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Dermatitis allergic	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.97	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Drug hypersensitivity	5	0.8	0 (0.0)	2 (40.0)	24	1.32	2 (8.3)	6 (25.0)	2	0.06	0 (0.0)	0 (0.0)	10	0.19	0 (0.0)	4 (40.0)
Drug reaction with eosinophilia and systemic symptoms	0	-	0 (0.0)	0 (0.0)	1	0.66	0 (0.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Erythema nodosum	0	-	0 (0.0)	0 (0.0)	1	4.44	0 (0.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Eye edema	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	1.48	0 (0.0)	1 (100.0)
Eye swelling	2	1.81	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	4	1.5	1 (25.0)	1 (25.0)	6	0.86	0 (0.0)	0 (0.0)
Gingival swelling	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.61	0 (0.0)	0 (0.0)
Hypersensitivity	7	2.41	0 (0.0)	2 (28.6)	38	4.34	1 (2.6)	3 (7.9)	49	7.67	0 (0.0)	9 (18.4)	51	2.5	0 (0.0)	5 (9.8)
Infusion-related reaction	12	28.93	1 (8.3)	5 (41.7)	34	22.44	0 (0.0)	9 (26.5)	52	48.71	5 (9.6)	15 (28.8)	40	11.17	1 (2.5)	2 (5.0)
Injection-related reaction	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	1.82	0 (0.0)	0 (0.0)
Injection-site urticaria	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	2	0.26	0 (0.0)	0 (0.0)
Laryngospasm	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	7.6	0 (0.0)	0 (0.0)	1	2.49	0 (0.0)	1 (100.0)
Lip edema	1	30.16	0 (0.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Lip swelling	3	4.23	0 (0.0)	2 (66.7)	4	1.46	0 (0.0)	0 (0.0)	5	2.56	0 (0.0)	1 (20.0)	3	0.4	0 (0.0)	1 (33.3)
Mouth swelling	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.3	0 (0.0)	1 (100.0)
Pharyngeal edema	2	3.62	0 (0.0)	0 (0.0)	2	0.82	0 (0.0)	0 (0.0)	2	1.06	0 (0.0)	0 (0.0)	4	0.98	0 (0.0)	0 (0.0)
Pharyngeal swelling	0	-	0 (0.0)	0 (0.0)	2	5.68	0 (0.0)	0 (0.0)	1	2.25	0 (0.0)	0 (0.0)	2	2.4	0 (0.0)	1 (50.0)
Rash	2	0.16	0 (0.0)	0 (0.0)	34	1.54	0 (0.0)	10 (29.4)	15	0.74	0 (0.0)	1 (6.7)	103	2.26	0 (0.0)	3 (2.9)
Rash erythematous	1	0.65	0 (0.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	4	0.57	0 (0.0)	0 (0.0)
Rash generalized	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Rash macular	0	-	0 (0.0)	0 (0.0)	2	0.51	0 (0.0)	0 (0.0)	1	0.2	0 (0.0)	0 (0.0)	4	0.61	0 (0.0)	0 (0.0)
Rash pruritic	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.13	0 (0.0)	0 (0.0)	6	0.7	0 (0.0)	0 (0.0)
Rash vesicular	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	0.62	0 (0.0)	0 (0.0)

Table 1 (continued)

AE	Iron dextran			Iron sucrose			Ferumoxytol			Ferric carboxymaltose						
	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)	Cases	ROR05	Deaths, n (%)	Hosp., n (%)
Scrotal edema	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	4.69	0 (0.0)	0 (0.0)
Serum sickness	1	12.07	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	1.16	0 (0.0)	1 (100.0)
Shock	0	-	0 (0.0)	0 (0.0)	1	0.64	0 (0.0)	0 (0.0)	1	0.82	1 (100.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)
Stevens-Johnson syndrome	1	2.73	1 (100.0)	1 (100.0)	1	0.62	0 (0.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Swelling face	2	1.18	0 (0.0)	1 (50.0)	4	0.76	0 (0.0)	0 (0.0)	4	0.97	0 (0.0)	1 (25.0)	8	0.81	0 (0.0)	0 (0.0)
Swollen tongue	1	0.81	0 (0.0)	0 (0.0)	7	3.64	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	8	1.82	0 (0.0)	2 (25.0)
Tongue edema	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	2.89	0 (0.0)	0 (0.0)
Toxic epidermal necrolysis	1	6.7	1 (100.0)	1 (100.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Type I hypersensitivity	0	-	0 (0.0)	0 (0.0)	1	9.14	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)
Type IV hypersensitivity reaction	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	0	-	0 (0.0)	0 (0.0)	1	2.29	0 (0.0)	1 (100.0)
Urticaria	10	4.51	0 (0.0)	2 (20.0)	58	8.35	0 (0.0)	5 (8.6)	13	1.79	0 (0.0)	1 (7.7)	143	9.47	0 (0.0)	4 (2.8)

AEs adverse events, Hosp. hospitalization, ROR05 reporting odds ratio lower bound, SMQ Standardized Medical Query

^aAll individual Preferred Terms listed fell within the hypersensitivity narrow SMQ; Preferred Terms falling within the anaphylactic reaction narrow SMQ were anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, circulatory collapse, shock, and Type I hypersensitivity

Bold values show cases ≥ 5 and ROR05 ≥ 1, which was considered as a signal of a likely drug-AE association

were similarly elevated between male and female patients within each IV iron preparation, but were lowest with ferric carboxymaltose in both male and female patients (Table S4 of the ESM). ROR05 values for hospitalization due to SMQ hypersensitivity or an SMQ anaphylactic reaction were higher among male vs female patients for iron sucrose and ferumoxytol. There were too few deaths in each subgroup to make any meaningful comparison between ROR05 values for deaths by age group or sex. We did not identify any evidence of masking: all MRCI values were close to unity (Table S5 of the ESM).

5 Medical Costs Associated with Managing AEs of IV Iron Preparations

A breakdown of costs for each iron preparation is summarized in Table 2 (a breakdown of costs applied to each AE is summarized in Table S6 of the ESM) and total medical cost estimates associated with AEs of iron preparations are summarized in Table 3. For the time period examined, ferumoxytol had the highest total downstream medical costs associated with anaphylaxis and manifestations of hypersensitivity reactions (US\$1,240,963), followed by iron sucrose (US\$724,544), ferric carboxymaltose (US\$650,431), and iron dextran (US\$422,137).

When expressed as average costs for each iron preparation per AE, which accounts for differing reporting rates among the preparations, the highest medical costs per AE (all hypersensitivity reactions) occurred with iron dextran (US\$8615) and ferumoxytol (US\$8164), followed by iron sucrose (US\$4212) and ferric carboxymaltose (US\$1832). Medical cost estimates associated with anaphylaxis were higher than those associated with hypersensitivity reactions without anaphylaxis (Table 3), with the highest medical costs per anaphylaxis AE occurring with ferumoxytol (US\$9896).

When expressed as average costs for each iron preparation per the estimated total number of patients treated with these preparations, ferumoxytol had the highest average costs (all hypersensitivity reactions) per treated patient (US\$1.24), followed by iron dextran (US\$0.61), ferric carboxymaltose (US\$0.55), and iron sucrose (US\$0.17). The same pattern was evident for average costs per treated patient for hypersensitivity reactions without anaphylaxis and for anaphylaxis (Table 3).

6 Discussion

The major finding from this FAERS database study is that there are differential reporting rates of hypersensitivity and anaphylactic reactions for the four studied IV iron products;

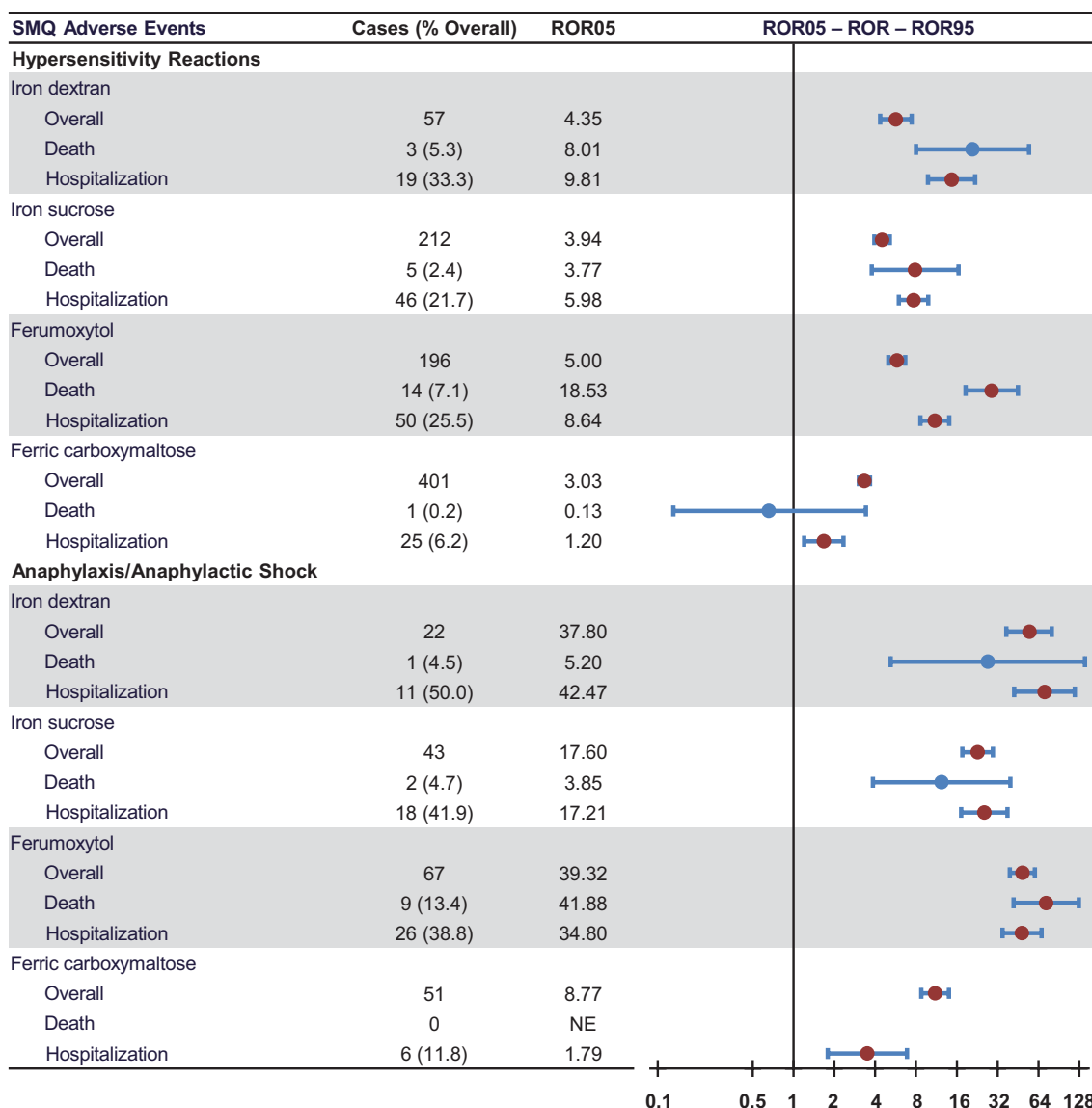


Fig. 1 Primary suspect case counts and disproportionality associated with adverse events (AEs) of interest (Standardized Medical Query [SMQ] terms) and death and hospitalizations associated with those AEs reported in the USA from 1 January, 2014 to 31 December, 2019. Data shown are primary suspect case counts and disproportional

ity (reporting odds ratio [ROR] with upper [ROR95] and lower bounds [ROR05] of the 90% confidence interval) associated with AEs of interest. Events with cases ≥ 5 and ROR05 ≥ 1 were considered as a signal for a likely drug–AE association

reporting rates were highest for ferumoxytol and iron dextran, intermediate for iron sucrose, and lowest for ferric carboxymaltose. This finding from the national US spontaneous reporting system, FAERS, is consistent with prior real-world studies, both using spontaneous reporting databases and claims databases [4, 8, 15, 16]. In addition, our analysis used the ROR, which is less likely to result in biased estimates than other disproportionality measures [31], as well as providing new cost estimates associated with these AEs. This type of assessment differs from clinical trials, which

are designed to increase the likelihood that drug efficacy signals can be detected. Specifically, most inclusion and exclusion criteria of clinical trials are designed to include a relatively homogenous study population, that may comprise individuals at lower risk of AEs. For example, a head-to-head clinical trial whose primary endpoint was evaluation of safety, and specifically hypersensitivity and anaphylactic reactions, among patients treated with either ferumoxytol or ferric carboxymaltose, excluded patients with a prior history of allergies to drugs that did not include those under

investigation [12]. This, together with the small sample sizes in most clinical trials, means that uncommon yet clinically important AEs may not be detected before drug approval. Therefore, careful post-approval monitoring is vital to the ongoing safety evaluation of approved therapies. The FDA professionals and pharmacovigilance experts routinely look to the FAERS data for post-marketing drug safety surveillance and as a guide to and signal generator of drug safety issues [43].

Approved IV iron preparations are an important component of current therapeutic armamentariums [2], but are known to be associated with rare and/or serious hypersensitivity reactions and anaphylaxis [4, 5]. Using a disproportionality analysis of FAERS primary suspect cases, we found that all IV iron preparations were associated with signals for overall hypersensitivity and anaphylactic reactions, but ROR05 values were highest for ferumoxytol and iron dextran followed by iron sucrose, with ferric carboxymaltose having the lowest ROR05 values. Signals for death associated with hypersensitivity and anaphylactic reactions were present for ferumoxytol, whereas only one death associated with a hypersensitivity reaction occurred with ferric carboxymaltose. Signals for hospitalization associated with hypersensitivity and anaphylactic reactions were present for ferumoxytol, iron dextran, and iron sucrose, with ferric carboxymaltose having the lowest ROR05 value. Reporting rates were also lowest with ferric carboxymaltose in various supplementary analyses, including an analysis of total suspect case counts and analyses of primary case counts stratified by age group and sex. In addition, these lower reporting rates with ferric carboxymaltose results could not be explained by masking owing to the presence of other IV iron preparations reporting similar AEs in the same database; MRCI values were all very close to unity.

An alternative assessment of a drug's potential safety risk can be achieved by estimating the magnitude of downstream direct medical costs based on AE and outcome costing data using the methods of Hoffman et al. [43]. These methods provide an accessible reference point regarding real-world differences in post-marketing drug safety [43]. The results obtained can be used to improve patient safety by identifying therapies that cause an undue burden on patients and healthcare providers. The current analyses showed that over the time period examined, total downstream medical costs associated with anaphylaxis and manifestations of hypersensitivity reactions were highest with ferumoxytol (US\$1,240,963). Total costs were about 42–66% lower with the three other IV iron preparations. When average costs per AE were considered, which accounts for differences in AE reporting rates, iron dextran and ferumoxytol were associated with the highest costs per AE (US\$8615 and US\$8164, respectively). When average costs per treated patient associated with these AEs were considered, ferumoxytol again had

the highest cost, followed by iron dextran, ferric carboxymaltose, and iron sucrose. Thus, using the system of Hoffman et al. [43], results suggest that ferumoxytol is associated with the greatest burden of anaphylaxis and manifestations of hypersensitivity reactions, and that ferric carboxymaltose and iron sucrose are associated with the lowest burden of these events. The low burden of events with ferric carboxymaltose is not unexpected because this preparation is characterized by a tight binding of elemental iron to the carbohydrate polymer shell [7] and has the lowest labile-free iron release of the IV iron preparations considered [47].

While real-world studies, both using spontaneous reporting databases and claims databases have shown results consistent with our analysis [4, 8, 15, 16], other analyses have not [11]. In a meta-analysis of randomized controlled trials examining AEs across trials comparing ferumoxytol with other pooled IV iron preparations (iron sucrose and ferric carboxymaltose), oral iron, and placebo, an elevated rate of hypersensitivity reactions and hypotension was noted with ferumoxytol vs oral iron, but not vs the pooled IV iron group. However, only three studies contributed to this latter comparison and all three studies specifically excluded patients with a prior history of allergies to drugs that did not include those under investigation [11]. In an earlier, but much larger, meta-analysis of 103 clinical trials, infusion reactions were increased with all IV iron preparations examined (iron sucrose, ferric gluconate, and ferric carboxymaltose) compared with placebo, oral iron, or no iron, and ferric carboxymaltose was associated with a reduced rate of cardiovascular AEs and AEs leading to discontinuation [13]. However, this analysis did not include ferumoxytol and made no comparisons among the IV iron preparations examined.

6.1 Limitations

A number of limitations of our analyses must be acknowledged. These analyses used FAERS data that have well-recognized limitations: the FDA does not require a causal relationship for an event to be reported; the “primary suspect” designation in FAERS is subjective; many AEs are not reported to FAERS; and reporting rates to FAERS are likely to be low in general, may not be similar across the included drugs, and may vary as a function of drug approval dates. Estimates of the impact of FAERS underreporting vary in the literature, but one study found that roughly 20–33% of the expected serious events were reported to FAERS for selected biologics and narrow therapeutics index drugs examined [48]. In addition, although reports lodged in FAERS are evaluated by clinical reviewers to monitor the safety of products after they are approved by the FDA, there is no certainty that the reported event was caused by a named product or that all AEs relating to a product are reported

Table 2 Breakdown of downstream medical costs associated with intravenous iron for AEs of interest (MedDRA® preferred terms) and number of cases of each AE reported in the USA from 1 January, 2014 to 31 December, 2019

AE	Iron dextran				Iron sucrose				Ferumoxytol				Ferric carboxymaltose							
	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total
Anaphylaxis/anaphylactic shock	17	\$31,084	\$59,456	\$49,762	\$140,302	31	\$62,989	\$136,174	\$75,100	\$274,264	60	\$243,591	\$191,443	\$161,199	\$596,234	43	\$0	\$38,291	\$194,155	\$232,445
Anaphylactic reaction	5	\$0	\$38,915	\$4,690	\$43,605	6	\$0	\$20,293	\$21,374	\$41,667	4	\$0	\$18,765	\$9,564	\$28,330	3	\$0	\$19,380	\$4,954	\$24,334
Anaphylactic shock	0	\$0	\$0	\$0	\$0	4	\$0	\$9,485	\$14,466	\$23,951	3	\$0	\$0	\$14,833	\$14,833	5	\$0	\$0	\$24,637	\$24,637
Anaphylactoid reaction	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$5,343	\$5,343	1	\$33,528	\$0	\$0	\$33,528	0	\$0	\$0	\$0	\$0
Shock	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$5,343	\$5,343	1	\$33,528	\$0	\$0	\$33,528	0	\$0	\$0	\$0	\$0
Hypersensitivity reactions	12	\$31,084	\$52,852	\$46,180	\$130,115	34	\$0	\$113,997	\$168,139	\$282,136	52	\$148,630	\$182,615	\$221,413	\$552,658	40	\$33,528	\$28,244	\$251,271	\$313,044
Infusion-related reaction	1	\$31,906	\$0	\$0	\$31,906	1	\$0	\$9,627	\$0	\$9,627	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0
Stevens-Johnson syndrome	1	\$61,856	\$0	\$0	\$61,856	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0
Toxic epidermal necrolysis	0	\$0	\$0	\$0	\$0	1	\$0	\$6,589	\$0	\$6,589	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0
Erythema nodosum	2	\$0	\$0	\$118	\$118	34	\$0	\$54,967	\$1,411	\$56,378	15	\$0	\$5,839	\$858	\$6,696	103	\$0	\$17,657	\$5,949	\$23,606
Rash	1	\$0	\$5,234	\$0	\$5,234	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	4	\$0	\$0	\$231	\$231
Rash erythematous	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0
Rash generalized	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0

Table 2 (continued)

AE	Iron dextran				Iron sucrose				Ferumoxytol				Ferric carboxymaltose							
	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total	No. of cases of AE	Death	Hosp.	Non-death, hosp. (ER visits)	Total
Rash macular	0	\$0	\$0	\$0	\$0	2	\$0	\$0	\$111	\$111	1	\$0	\$0	\$63	\$63	4	\$0	\$0	\$248	\$248
Rash pruritic	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$60	\$60	6	\$0	\$0	\$357	\$357
Rash vesicular	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$60	\$60
Dermatitis allergic	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$79	\$79	0	\$0	\$0	\$0	\$0
Urticaria	10	\$0	\$8,527	\$475	\$9,001	58	\$0	\$21,305	\$3,174	\$24,479	13	\$0	\$4,636	\$737	\$5,373	143	\$0	\$17,638	\$8,356	\$25,994
Injection-site urticaria	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	2	\$0	\$0	\$123	\$123
Laryngospasm	0	\$0	\$0	\$0	\$0	0	\$0	\$0	\$0	\$0	1	\$0	\$0	\$3,109	\$3,109	1	\$0	\$5,352	\$0	\$5,352

AE adverse event, ER emergency room, hosp. hospital, MedDRA® Medical Dictionary for Regulatory Activities

All monetary values are US\$

All costs were inflation adjusted on a yearly basis using the medical care services component of the consumer price index (not seasonally adjusted) for each month of December

[26]. However, we conducted a sensitivity analysis of total suspect case reports, regardless of attributed causality as in the primary suspect case analysis, and found similar results. Moreover, spontaneous reporting databases suffer from the general limitation that only a numerator is available, which may itself be subject to reporting bias. Therefore, in the absence of denominator information on the overall population exposed to the drug, the specific risk associated with the drug is difficult to estimate. While disproportionality measures aim to overcome this limitation by quantifying to what extent reported AEs are occurring more frequently than expected with a specific drug vs all drugs, they can only indicate differential reporting rates and not actual differences in the occurrence of the event [24, 25, 49]. Thus, spontaneous reporting databases are useful for signal detection [25], whereas other data sources should be used for signal validation or comparative safety—ideally large, adequately powered, randomized controlled trials, or in the case of rare events, large prospectively designed observational studies conducted in representative populations.

Another general limitation of a disproportionality analysis is potential masking, where a disproportionate signal for a given drug–event pair can be masked because of the presence of a disproportionate signal for another drug with the same event of interest in the same database [41]. However, our analysis of MRCI did not show any evidence of masking or dilution of the signal for any of the IV iron preparations examined. An additional general limitation is that information on demographic and pre-existing medical history is limited in spontaneous reporting databases, making adjustment for confounding factors difficult. Age and sex information is available in FAERS, and while this demographic information is limited, our stratified analyses by age group showed that reporting rates of anaphylaxis tended to be higher among patients aged ≥ 65 vs < 65 years for all IV iron preparations and reporting rates for hospitalization due to hypersensitivity or anaphylactic reactions with iron sucrose and ferumoxytol were higher among patients aged ≥ 65 vs < 65 years and among male vs female patients. Nevertheless, it is important to note that signals indicating a likely drug–AE association also occurred among patients aged < 65 years and among female patients, meaning that this analysis is relevant to patients of all ages and sex. However, these stratified analyses were limited by missing information on age and sex in 47.2% and 11.1% of cases, respectively. In addition, although outcome data are collected in FAERS, this information was missing in a substantial number of reports (e.g., for hospitalization and death in our analysis, coverage was only 42.8%); thus, this limitation should be acknowledged when assessing reporting rates for hospitalization and death in this analysis. Other relevant limitations specific to this analysis include the low number of overall reports with iron dextran during the timeframe of

Table 3 Aggregated medical costs associated with managing AEs of interest for intravenous iron preparations reported in the USA from 1 January 2014 to 31 December, 2019

	Death costs	Hospital costs	Non-death, hospital costs (ER visit)	Total costs	Total AEs	Average costs/AE	Total patients	Average costs/patient
Hypersensitivity reactions: including anaphylaxis/anaphylactic shock								
Iron dextran	\$155,929	\$164,983	\$101,225	\$422,137	49	\$8,615	695,827	\$0.61
Iron sucrose	\$62,989	\$372,437	\$289,119	\$724,544	172	\$4,212	4,268,967	\$0.17
Ferumoxytol	\$425,749	\$403,298	\$411,915	\$1,240,963	152	\$8,164	1,004,275	\$1.24
Ferric carboxymaltose	\$33,528	\$126,562	\$490,341	\$650,431	355	\$1,832	1,183,784	\$0.55
Hypersensitivity reactions: excluding anaphylaxis/anaphylactic shock								
Iron dextran	\$124,845	\$66,612	\$46,773	\$238,230	27	\$8,823	695,827	\$0.34
Iron sucrose	\$0	\$206,484	\$172,835	\$379,319	130	\$2,918	4,268,967	\$0.09
Ferumoxytol	\$148,630	\$193,090	\$226,319	\$568,038	84	\$6,762	1,004,275	\$0.57
Ferric carboxymaltose	\$33,528	\$68,891	\$266,596	\$369,015	304	\$1,214	1,183,784	\$0.31
Anaphylaxis/anaphylactic shock								
Iron dextran	\$31,084	\$98,371	\$54,453	\$183,907	22	\$8,359	695,827	\$0.26
Iron sucrose	\$62,989	\$165,952	\$116,283	\$345,225	42	\$8,220	4,268,967	\$0.08
Ferumoxytol	\$277,120	\$210,208	\$185,597	\$672,925	68	\$9,896	1,004,275	\$0.67
Ferric carboxymaltose	\$0	\$57,671	\$223,745	\$281,416	51	\$5,518	1,183,784	\$0.24

AE adverse event, *ER* emergency room

All monetary values are US\$

All costs were inflation adjusted on a yearly basis using the medical care services component of the consumer price index (not seasonally adjusted) for each month of December

the study. It is well known that reporting frequency varies as a function of time since approval, which should be considered when assessing iron dextran results (see Fig. S1 of the ESM). It is also possible that FDA boxed warnings concerning some IV iron preparations may have led to increased reporting.

Findings for the cost estimates may not be comprehensive because they were obtained by mapping AHRQ HCUP cost survey data to MedDRA[®] terms found in FAERS; not all FAERS hypersensitivity MedDRA[®] terms had an associated cost mapping available. Thus, potential variations between the FAERS patient population and those used for HCUP surveys could influence estimates. In addition, the most recent available data from the AHRQ HCUP cost survey data were from the year 2016 [32, 33], and for hospital stays resulting in death, the year 2007 [44]. Because of the limited available costing data, we operated on the assumption that the estimated hospitalization costs for the given AE remained the same year to year; however, we adjusted these calculations

for inflation on a yearly basis using the medical care services component of the consumer price index available from the US Bureau of Labor Statistics. We specifically analyzed downstream medical costs only as we wished to focus on costs attributable to AEs not confounded by the acquisition costs of the various IV iron preparations. Finally, patients reporting AEs for each IV iron preparation were not matched on baseline characteristics, thus differences in prescribing patterns could account for some differences in AEs (e.g., one preparation might be used more frequently for patients with comorbidities or severe iron deficiency anemia).

7 Conclusions

We found that although all the IV iron formulations we considered had signals for likely drug–AE associations based on ROR05 for hypersensitivity reactions and anaphylaxis, signals were highest for ferumoxytol and iron dextran,

intermediate for iron sucrose, and lowest for ferric carboxymaltose. When hospitalization and deaths associated with anaphylaxis or hypersensitivity reactions were considered, we found that the signal was highest for ferumoxytol and iron dextran, intermediate for iron sucrose, and lowest for ferric carboxymaltose. Downstream direct medical costs based on these AEs supported these findings. Results of this real-world analysis of FAERS data suggest that reporting rates of anaphylaxis and other hypersensitivity reactions among patients requiring an IV iron preparation are lowest with ferric carboxymaltose.

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Declarations

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Conflicts of interest/Competing interests Henry Trumbo is a consultant for American Regent, Daiichi Sankyo, and Allergan. Lawrence T. Goodnough is a consultant for American Regent. Karolina Kaluza and Syed Numan are employees of American Regent, the manufacturers of ferric carboxymaltose.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability The code used to conduct this analysis was provided by Evidex[®] (which is not publicly available), PostgreSQL (a free and open-source relational database), and Microsoft[®] Excel[®].

Availability of data and material The source data and analytics for this study were provided by Evidex[®], licensed by Advera Health Analytics, Inc., and are not publicly available. Healthcare Cost and Utilization Project data are made publicly available by the Agency for Healthcare Research and Quality.

Author contributions HT and LTG contributed to the interpretation of data, and to the reviewing and writing of the report. KK and SN contributed to the conception and design of the analysis, the interpretation of data, and to the reviewing and writing of the report. All authors read and approved the final version.

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