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ORIGINAL ARTICLE

Comparison of hypersensitivity reactions of intravenous iron: iron isomaltoside-1000 (Monofer®) versus ferric carboxy-maltose (Ferinject®). A single center, cohort study

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AIMS

Intravenous iron supplementation is widely used to treat iron deficiency and iron deficiency anemia when oral iron administration is ineffective or poorly tolerated. Hypersensitivity reactions (HSRs) during infusions are rare, but can be life-threatening. This study aimed to compare the risk for HSRs with the intravenous administration of iron isomaltoside-1000 and ferric carboxymaltose for the treatment of iron deficiency and iron deficiency anemia.

METHODS

This was a single-centre cohort study. Nurses and physicians were instructed to fill out an HSR registration form with every administration of intravenous iron. HSRs were distinguished into serious and non-serious HSRs using the Ring and Messmer classification.

RESULTS

HSRs occurred in 18/836 (2.1%) ferric carboxymaltose and 43/496 (8.7%) iron isomaltoside-1000 administrations. The crude risk for HSRs was 75% lower after ferric carboxymaltose treatment (RR = 0.248, 95% CI: 0.145–0.426, $P < 0.0001$). The risk for grade II HSRs was 88% lower after ferric carboxymaltoside (RR = 0.123, 95% CI: 0.051–0.294). The likelihood of HSRs was 3.4 times higher after the administration of iron isomaltoside-1000 (95% CI: 1.910–6.093, $P < 0.0001$). Regardless of the type of intravenous iron, patients with comorbidities have a factor 3.6 higher risk (95% CI: 1.899–6.739, $P < 0.0001$).

CONCLUSIONS

Ferric carboxymaltose is associated with a 75% lower risk for HSRs compared with iron isomaltoside-1000 in our population. The presence of a comorbidity raises the likelihood of an HSR by a factor of three regardless of the type of intravenous iron infusion. Further research is needed to clarify the underlying mechanism in various patient groups.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acute reactions during intravenous iron infusions have been reported for the (newly) approved iron formulations.
- The risk for hypersensitivity reactions after intravenous iron infusions is increased in patients with known allergies or immune or inflammatory conditions and in patients with a history of severe asthma, eczema or other atopic allergy.
- The European Medicines Agency (EMA) has published strict recommendations for the use of intravenous iron.

WHAT THIS STUDY ADDS

- Ferric carboxymaltose is associated with a 75% lower risk for hypersensitivity reactions compared with iron isomaltoside-1000 in our population.
- The presence of a comorbidity raises the likelihood of an HSR by a factor of three regardless of the type of intravenous iron infusion.
- Switching between two drug formulations is a potential occasion for observational research.

Introduction

Intravenous iron supplementation is widely used to treat iron deficiency and iron deficiency anaemia when oral iron administration is ineffective or poorly tolerated [1–3]. Intravenous iron is also administered in combination with erythropoiesis-stimulating agents to treat iron deficiency in chronic kidney disease and chemotherapy-induced anaemia. Acute reactions to intravenous iron infusions are rare, but when they occur, they can be life-threatening. The possibility of hypersensitivity reactions (including anaphylaxis) to high-molecular-weight iron dextran has traditionally limited the indications for the intravenous administration of iron. Newly approved iron formulations, like ferric carboxymaltose (Ferinject®) and iron isomaltoside-1000 (Monofer®), have the advantage of a lower risk for infusion reactions and can be given in a higher dose due to their lower molecular weight [4]. However, acute reactions have also been reported for these newly approved iron formulations [5].

In a large teaching hospital in Rotterdam, the Netherlands, both ferric carboxymaltose (up to and including 2012) and iron isomaltoside-1000 (since 2013) have been used to treat patients with iron deficiency and iron deficiency anaemia as the first drug of choice. In February 2013 ferric carboxymaltose was replaced by iron isomaltoside-1000 due to significantly lower drug costs. After the introduction of iron isomaltoside-1000, physicians expressed their concerns about the safety, reporting infusion reactions, dyspnoea, palpitations, nausea and headache. An evaluation revealed six hypersensitivity reactions (HSRs) in 66 administrations of iron isomaltoside-1000 (9.1%). This percentage corresponds with information on HSRs available from the summary of product characteristics (SPC) of isomaltoside-1000 and ferric carboxymaltose [6, 7]. Following these experiences with regard to HSRs to iron isomaltoside-1000 in 2013, our hospital switched back to ferric carboxymaltose in January 2014.

In November 2013 the European Medicines Agency (EMA) published an assessment report based on concerns regarding hypersensitivity reactions of products containing intravenous iron. The EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimize the risk of allergic reactions. As a result, the EMA published strict recommendations for the use of intravenous iron:

- All prescribers should inform patients of the risk and seriousness of a hypersensitivity reaction and the importance of seeking medical attention if a reaction occurs.
- The risk of hypersensitivity is increased in patients with known allergies or immune or inflammatory conditions and in patients with a history of severe asthma, eczema or other atopic allergy [8].

A PubMed search using the terms 'ferric carboxymaltose', 'iron isomaltoside-1000' and 'hypersensitivity' as subject headings or mentioned in the title or abstract showed that comparative studies of HSRs of the newer intravenous iron formulations, specifically ferric carboxymaltose and iron isomaltoside-1000, are very limited [9]. Bager *et al.* [9] found a higher risk of mild HSRs with iron isomaltoside-1000 administration when compared to ferric carboxymaltose administration. However, only patients from the Department of Hepatology and Gastroenterology were included in this study, and factors associated with the occurrence of HSRs were not investigated.

Based on the assumption of more HSRs with iron isomaltoside-1000 administrations and the lack of evidence, we initiated a comparative study of hypersensitivity reactions of iron isomaltoside-1000 and ferric carboxymaltoside. The aim of the study was to compare the risk for HSRs with the intravenous administration of iron isomaltoside-1000 and ferric carboxymaltose for the treatment of iron deficiency and iron deficiency anaemia in daily clinical practice. Also, factors associated with the occurrence of HSRs were investigated.

Methods

Design and patients

Our study was a single centre cohort study conducted at the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. Intravenous administration of iron isomaltoside-1000 was given between 1 February 2013 and 31 December 2013 and ferric carboxymaltose between 1 January 2014 and 31 December 2014 for the treatment of iron deficiency and iron deficiency anaemia.

Included were all patients with one or more administrations of iron isomaltoside-1000 or ferric carboxymaltose between February 2013 and December 2014. Patients on dialysis were excluded, because the first drug of choice for

these patients in this period was iron sucrose (Venofer®) in our hospital. Furthermore, patients with known allergies to intravenous iron were excluded.

The study was approved by our institutional review board and did not fall under the Medical Research Involving Human Subjects Act (WMO).

Interventions

Iron isomaltoside-1000 and ferric carboxymaltose were used at a dosage of 1000 mg. Iron isomaltoside-1000 was administered in 60 min and ferric carboxymaltose was administered in 15 min, according to manufacturer's instructions [6, 7].

Data collection

An HSR registration form was developed to record (suspected) HSRs prospectively. The form was based on a checklist 'Adverse Events' provided by the pharmaceutical company of iron isomaltoside-1000. Nurses and physicians were instructed to fill out the HSR registration form for every administration of ferric carboxymaltose or iron isomaltoside-1000 in the study period. The HSR registration form was used to register patient information, name of the iron formulation used, date of administration and indication. In case of a (suspected) HSR, the nurse or the physician had to complete the form with the description of the reaction, time to the reaction (in minutes) since administration, clinical information (e.g. blood pressure, heart rate), clinical course after the onset of the reaction and the history of previous intravenous iron administrations.

Later, it appeared that not all HSR registration forms were filled out for every administration of intravenous iron in the study period. To avoid the risk of selection bias, we retrospectively identified all intravenous iron administrations in the study period through the hospital's electronic medical registry (ChipSoft) and added the missing data to the prospectively collected data. The following information was collected from the patients' electronic medical records: sex, age, department, diagnosis, dose, type of intravenous iron given, administration date, presence of comorbidities, history of intravenous iron and any data on HSRs and complications. Intravenous iron administrations accidently registered twice on the same date in the hospital's electronic medical registry were excluded.

Causal relationship and hypersensitivity reaction classification

Causal relationship between the administration of intravenous iron and HSRs was determined for every reaction using the Naranjo score [10].

HSRs were distinguished into serious and non-serious HSRs using the Ring and Messmer classification (see Table 1) [11]. To reduce interrater variability, all HSRs were independently categorized by a panel of two pharmacists (M.B.M. and H.L.v.d.H.) and one physician (A.J.P.v.T.). Next, their grades were compared and when dissensus existed, the panel members reviewed their own classifications and discussed until consensus was reached about the grade. All HSRs were also reported to the Netherlands Pharmacovigilance Centre Lareb.

Table 1

Ring and Messmer classification

Grade	Symptoms
I	Skin symptoms and or mild fever reaction
II	Measurable, but not life threatening Cardiovascular reaction (tachycardia, hypotension) Gastrointestinal disturbance (nausea) Respiratory
III	Shock, life-threatening spams of smooth muscles (bronchi, uterus)
IV	Cardiac and or respiratory arrest

Statistical methods

No formal sample size calculation was performed. We included all patients in the analyses that received at least one intravenous iron administration during the study period.

Variables were described with descriptive statistics: *n* (%) for nominal and ordinal variables and mean (95% confidence interval, CI) or median (inter-quartile range, IQR) for the continuous variables, depending on the shape of the distribution.

Table 2

Baseline characteristics

	Ferric carboxymaltose (*n* = 836)	Iron isomaltoside-1000 (*n* = 496)
Age (year) (median, IQR)	50.2 (34.1–73.6)	53.2 (36.0–74.4)
Sex		
Female	612 (73.2%)	369 (74.4%)
Male	224 (26.8%)	127 (25.6%)
Departments		
Gastroenterology	231 (27.6%)	223 (44.9%)
Gynaecology	155 (18.5%)	34 (6.9%)
Internal Medicine	259 (31.0%)	188 (37.9%)
Other[a]	191 (22.8%)	51 (10.3%)
Presence of a comorbidity[b]		
Gastrointestinal	77 (9.2%)	82 (16.5%)
Pulmonary	32 (3.8%)	37 (7.5%)
Dermatological	30 (3.6%)	15 (3.0%)
Rheumatological	24 (2.9%)	15 (3.0%)
Other[c]	7 (0.84%)	5 (1.0%)

IQR, inter-quartile range

[a]Other includes cardiology, surgery, urology, dermatology, rheumatology, pediatrics, and ophthalmology, and the care hotel located near the hospital

[b]Comorbidity: registered comorbidities at every administration of intravenous iron. Every comorbidity is counted separately

[c]Other includes immunological and haematological comorbidities

The excess risk of complications with ferric carboxymaltose relative to iron isomaltoside-1000 treatment was expressed as relative risk (RR, with 95% CI) for the total patient group, as well as for the following subgroups: grade according to Ring and Messmer classification, time to occurrence and presence of comorbidity. Risk factors associated with the occurrence of HSRs were investigated using multiple binary logistic regression analysis. The dependent variable was the occurrence of an HSR. Covariables were age, sex, type of intravenous iron, presence of a comorbidity and type of department. The logistic regression analysis was repeated with type of department as strata (internal medicine/gastroenterology/other and gynaecology) to adjust for possible multicollinearity between age, gender and department. Due to multiple testing, a two-sided *P*-value of <0.0125 was considered to indicate statistical significance. Statistical software PASW Statistics 25 was used for analysis.

Results

Patients and intravenous iron administrations

During the study period, intravenous iron was administered 1332 times. Of these, 496/1332 (37.2%) administrations were iron isomaltoside-1000 and 836/1332 (62.8%) ferric carboxymaltose. The HSR registration form was filled in prospectively for 327 of 496 (65.9%) administrations of iron isomaltoside-1000 and 304 of 836 (36.4%) administrations of ferric carboxymaltose.

Table 2 presents patients' baseline characteristics. Approximately 70% of intravenous iron administrations were given to females, iron isomaltoside-1000 was more frequently used in the Department of Gastroenterology and ferric carboxymaltose was more frequently used in the Department of Gynaecology. In the iron isomaltoside-1000 group, 154/496 (31%) of the patients with an iron infusion had a comorbidity *vs*. 170/836 (20.3%) in the ferric carboxymaltose group. Patients with a gastrointestinal comorbidity received iron isomaltoside-1000 more frequently.

Hypersensitivity reactions

Table 3 presents an overview of the HSRs for each intravenous iron formulation. The relative risk for HSRs was significantly lower for ferric carboxymaltose treatment (RR = 0.248, 95% CI: 0.145–0.426, $P < 0.0001$).

The most common HSRs were Ring & Messmer classification grades I and II. Three patients in the iron isomaltoside-1000 group experienced a grade III reaction, no grade IV reactions occurred and most of the patients in the iron isomaltoside-1000 group experienced HSRs within 30 min after the start of the infusion (see Table 3). The relative risk on grade I complications was not significantly higher in the iron isomaltoside-1000 group (RR = 0.647, 95% CI: 0.289–1.456).

Table 3

Overview of the hypersensitivity reactions (HSRs) in patients treated with ferric carboxymaltose or iron isomaltoside-1000, overall, and by Ring and Messmer classification, time to occurrence and Naranjo score

	Ferric carboxymaltose (*n* = 836)	**Iron isomaltoside-1000 (*n* = 496)**	**RR (95% CI)**
Total no. of HSRs	18	43	
Risk on HSR (95% CI)	2.1% (1.1–3.2%)	8.7% (6.1–11.2%)	0.248 (0.145–0.426) $P < 0.0001$
Ring and Messmer classification[a]			
Grade I	12 (66.7%)	11 (25.6%)	0.647 (0.289–1.456)
Grade II	6 (33.3%)	29 (67.4%)	0.123 (0.051–0.294)
Grade III	-	3 (6.9%)	n.a.
Time to occurrence			
< 5 min	2 (11.1%)	14 (32.6%)	0.085 (0.019–0.371)
5–30 min	4 (22.2%)	15 (34.9%)	0.158 (0.053–0.474)
> 30 min	4 (22.2%)	12 (27.9%)	0.198 (0.064–0.610)
Unknown	8 (44.4%)	2 (4.7%)	2.373 (0.506–11.13)
Naranjo Score			
Definite HSR	-	-	n.a.
Probable HSR	18 (100%)	43 (100%)	n.a.
Possible HSR	-	-	n.a.
Doubtful HSR	-	-	n.a.

n.a., not applicable; RR, Relative Risk; *P*-value of <0.0125 indicates statistical significance; HSR, hypersensitivity reaction
[a]No grade IV reactions occurred

The results of grade II complications indicate a significantly reduced risk of grade II HSRs after ferric carboxymaltose administration (RR = 0.123, 95% CI: 0.051–0.294).

In every patient the infusion was stopped after an HSR occurred and clemastine was administered. All patients recovered. In addition, in 20 patients the infusion of intravenous iron was successfully resumed at a lower infusion rate after the HSR occurred, seven patients switched directly after the HSR to a different intravenous iron formulation with success, and 13 patients received a different intravenous iron formulation successfully several months/years after the HSR. Lastly, seven patients with an HSR on iron isomaltoside-1000 had previously received an infusion with ferric carboxymaltose without any problems. One patient with an HSR on ferric carboxymaltose had previously received an infusion with iron isomaltoside-1000 without any problem. Two patients reported an HSR > 24 h after the infusion.

All HSRs are determined as probable by the Naranjo score.

HSRs by subgroup

Table 4 presents an overview of the HSRs by subgroup for each intravenous iron formulation. More females experienced an HSR and the age of most females was between 30 and 50 years.

Table 4

Overview of the hypersensitivity reactions (HSRs) by subgroup

	Ferric carboxymaltose (*n* = 836)	Iron isomaltoside-1000 (*n* = 496)
Total no. of HSRs	18 (2.2%)	43 (8.7%)
Sex		
Male	2	2
Female	16	41
Age (year) male and female		
Mean age (median, IQR)	32.5 (28.3–46.3)	32.9 (27.3–43.5)
<30	4	13
30–≤50	12	22
>50	2	8
Age (year) male		
Mean age (median, IQR)	59.1 (47.8–70.4)	35.0 (16.8–53.2)
<30	-	1
30–≤50	1	-
>50	1	1
Age (year) female		
Mean age (median, IQR)	31.0 (26.8–44.5)	32.9 (27.7–42.7)
<30	4	12
30–≤50	11	22
>50	1	7

IQR, inter-quartile range; n.a. = not applicable

In the iron isomaltoside-1000 group, more comorbidities were registered, 22 of the 43 administrations with an HSR, while in the ferric carboxymaltose group comorbidities were registered for three of the 18 administrations with an HSR (RR = 0.081, 95% CI: 0.024–0.269). For the iron isomaltoside-1000 group, 9 out of 22 comorbidities appeared to be gastrointestinal comorbidities.

Factors associated with the occurrence of HSRs

Table 5 presents an overview of the factors associated with the occurrence of HSRs. Overall, the presence of a comorbidity, iron isomaltoside-1000 administration and age increased the risk of an HSR significantly. The presence of a comorbidity raises the incidence of an HSR by a factor of 3.6 (OR = 3.577), usage of iron isomaltoside-1000 increases the risk of HSR manifestations by a factor of 3.4 (OR = 3.411), and the risk of the occurrence of an HSR is approximately 4% lower for every year older a patient is (OR = 0.956). Males are associated with a lower risk for the occurrence of an HSR of approximately 75% (OR = 0.245) compared to females.

More specifically, in patients from the departments of Internal Medicine, Gastroenterology and Other, a significant effect on HSR manifestations is seen with the presence of a comorbidity (OR = 2.775), with the usage of iron isomaltoside-1000 (OR = 3.785) and a younger age (OR = 0.953) (Table 5). In patients from the Department of Gynaecology, presence of a comorbidity showed a significant effect on the occurrence of an HSR (OR = 10.072) (Table 5).

Discussion

This study is to our knowledge the largest cohort study comparing HSRs after iron isomaltoside-1000 and ferric carboxymaltose administrations. The risk for HSRs was almost 75% (RR = 0.248) and the risk for Ring & Messmer grade II HSRs was about 88% (RR = 0.123) lower after ferric carboxymaltose treatment. The presence of a comorbidity raises the likelihood of an HSR by a factor of 3.6. Also, usage of iron isomaltoside-1000 and younger age increased the risk of an HSR.

Our study is in line with the EMA assessment report regarding a higher risk for HSR due to comorbidities and the study performed by Bager *et al.*, showing a higher risk of mild HSRs with iron isomaltoside-1000 administration when compared to ferric carboxymaltose administration [8, 9]. Patients in our cohort had a wide range of comorbidities and it is known that certain comorbidities can increase the risk of hypersensitivity reactions [8]. However, it remains unclear whether the risk of hypersensitivity reactions is due to the intravenous iron formulation itself or to the allergies, immune system, inflammatory diseases or other patient conditions. Hypersensitivity reactions caused by intravenous iron formulations are attributed by some experts to the effects of bioactive labile iron. All intravenous iron formulations currently approved by regulatory authorities consist of iron-carbohydrate structures. The formulations differ from each other by the size of the core, the identity and the density of the surrounding carbohydrate. These

Table 5

Overview of factors associated with the occurrence of hypersensitivity reactions (HSRs)

	All departments (*n* = 1332)OR (95% CI)	Departments of internal medicine, gastroenterology, and other[b] (*n* = 1143)OR (95% CI)	Department of gynaecology (*n* = 189)OR (95% CI)
Age (year)	0.956 (0.939–0.972)$P < 0.0001$	0.953 (0.936–0.970)$P < 0.0001$	1.002 (0.933–1.076)$P > 0.950$
Sex			
Male *vs.* female	0.245 (0.083–0.719)$P = 0.01$	0.252 (0.086–0.743)$P = 0.012$	n.a.
Type intravenous iron			
Iron isomaltoside-1000 *vs.* ferric carboxymaltose	3.411 (1.910–6.093)$P < 0.0001$	3.785 (1.964–7.293)$P < 0.0001$	2.031 (0.448–9.219)$P = 0.359$
Presence of a comorbidity[a]			
Presence of a comorbidity[a]	3.577 (1.899–6.739)$P < 0.0001$	2.775 (1.398–5.512)$P = 0.004$	10.072 (2.404–42.202)$P = 0.002$
Departments			
Department gastroenterology *vs.* other[b]	0.854 (0.261–2.789)$P = 0.794$	0.897 (0.274–2.944)$P = 0.858$	n.a.
Department internal medicine *vs.* other[b]	2.424 (0.795–7.394)$P = 0.120$	2.292 (0.751–6.996)$P = 0.145$	n.a.
Department gynaecology *vs.* other[b]	1.536 (0.447–5.284)$P = 0.496$	n.a.	n.a.

CI, confidence interval; n.a., not applicable; OR, odds ratio; *P*-value of <0.0125 indicates statistical significance

[a]Comorbidity: registered comorbidities at every administration of intravenous iron. Every comorbidity is counted separately

[b]Other includes cardiology, surgery, urology, dermatology, rheumatology, paediatrics, and ophthalmology, and the care hotel located near the hospital

differences determine the amount of labile iron that is released. Whether the amount of bioactive labile iron between iron isomaltoside-1000 and ferric carboxymaltose differs substantially, possibly resulting in clinically relevant differences in HSRs, is unknown [12, 13]. Moreover, the immunologic basis of allergic hypersensitivity to the newer iron agents still remains unknown [14]. The two main theories are immunological IgE-mediated responses and complement activation-related pseudo-allergy [15–17]. However, there are data that support the concept of IgE-mediated hypersensitivity only for intravenous iron dextran therapy and not for the newer carbohydrate formulations [18, 19].

Recently, two systematic reviews and meta-analysis of randomized clinical trials comparing intravenous iron to another comparator showed that all currently available intravenous iron preparations appear to be safe [20, 21]. However, the study by Rognoni *et al*. [21] did not include trials with iron isomaltoside-1000 and the study by Avni *et al*. [20] included just one trial with iron isomaltoside-1000. Furthermore, the reviews included randomized clinical trials comparing intravenous iron with oral iron, placebo, intramuscular iron or no iron. No trials directly comparing ferric carboxymaltose with iron isomaltoside-1000 were included because they were not published at that time [20, 21].

In our study, patients treated with iron isomaltoside-1000 had more comorbidities compared to patients treated with ferric carboxymaltose (31% *vs*. 20%). Most comorbidities were gastrointestinal. This is probably due to the fact that intravenous iron was mainly used in the Departments of Gastroenterology and Internal Medicine in our hospital. Interestingly, approximately 90% more HSRs were reported after administrations of iron isomaltoside-1000 in patients with a comorbidity (RR = 0.081). Moreover, irrespective of the intravenous iron formulation used, the presence of a comorbidity increased the occurrence rate of an HSR significantly by at least a factor of 2.8.

Another factor that seems to have an influence on the occurrence of HSRs is age. In the Department of Gynaecology, age did not have a significant influence. This is probably due to the fact that almost all patients treated in the Department of Gynaecology were between 30 and 50 years of age. However, for all patients, and specifically patients from the Departments of Internal Medicine, Gastroenterology and other, younger patients were at significantly higher risk of developing an HSR.

Finally, regarding sex, we observed a 75% reduced risk in the occurrence of HSRs in male patients after the administration of intravenous iron (OR = 0.245). However, in this study mainly females were included, which possibly underestimates the risk of the occurrence of HSRs in male patients. Nevertheless, also in the study by Bager *et al*. mainly females were included [9].

The strengths of our study are the real-life clinical setting, the long period (approximately 2 years) over which all intravenous iron administrations were evaluated, and the fact that the HSRs were independently categorized. Another strength is the fact that we also investigated factors associated with the occurrence of HSRs. These factors can guide physicians in their choice for the administration of intravenous iron in specific patients in clinical practice.

Our study has some limitations. During the study period, more ferric carboxymaltose administrations have been registered in comparison to iron isomaltoside-1000. This might be explained by the fact that in recent years intravenous iron is more commonly prescribed in our hospital. We noticed a rise of 25% in prescriptions for intravenous iron from 2012 up to and including 2014. Furthermore, patients included in this study seem to differ with regard to the department where the intravenous iron was administered. Most importantly, information bias might be present: the fact that nurses and physicians in our hospital already had experience with ferric carboxymaltose before we switched to iron isomaltoside-1000 might have caused higher awareness of HSRs after isomaltoside-1000 administrations. Additionally, our HSR registration started after the first reactions of iron isomaltoside-1000 were reported to the hospital pharmacy. Also, the EMA assessment report published 10 months after the introduction of our HSR registration study could have caused higher awareness of HSRs among the nurses and physicians in our hospital. On the other hand, we noticed a decrease in the number of filled out HSR registration forms during the study period, which points towards a reduced awareness among the nurses and physicians.

Conclusions

Ferric carboxymaltose is associated with a 75% lower risk for HSRs compared with iron isomaltoside-1000 in our population. The presence of a comorbidity, as independent risk-modifying factor, raises the likelihood of an HSR by a factor of three regardless of the type of intravenous iron infusion. Further research is needed to clarify the underlying mechanism in different patient groups.

Competing Interests

This study was an investigator-initiated, industry-independent study. There was no remuneration for investigators or subjects.

Contributors

M.B.M. made substantial contributions to acquisition of data, analysis and interpretation of data, and was involved in drafting the manuscript. H.L.v.d.H. made substantial contributions to the conception and design of the study, acquisition and interpretation of data, and was involved in revising the manuscript critically for important intellectual content. E.B. made substantial contributions to the analysis and interpretation of data, and was involved in revising the manuscript critically for important intellectual content. A.J.P.v.T. made substantial contributions to interpretation of data, and was involved in revising the manuscript critically for important intellectual content. E.M.W. made substantial contributions to acquisition and interpretation of data, and was involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. The principal investigator for this paper is E.M.W. and that she had direct clinical responsibility for patients.

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