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ORIGINAL RESEARCH

A systematic literature review and indirect comparison of iron isomaltoside and ferric carboxymaltose in iron deficiency anemia after failure or intolerance of oral iron treatment

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ABSTRACT

Objectives: The efficacy of oral iron in treating iron deficiency anemia (IDA) can be limited by poor gastrointestinal (GI) absorption and adverse GI symptoms; intravenous (IV) iron is a well-established alternative. The present study compared the efficacy of two IV iron formulations in patients with IDA: iron isomaltoside (IIM) and ferric carboxymaltose (FCM).

Methods: A systematic literature review (SLR) was conducted to identify randomized controlled trials (RCTs) of IIM and FCM in patients with IDA. An adjusted indirect treatment comparison (ITC) of IIM and FCM was then conducted to evaluate differences in change from baseline hemoglobin and the proportion of patients achieving a clinically-relevant response.

Results: The SLR identified no completed RCTs of IIM versus FCM, 5 RCTs of IIM (4 versus oral iron and 1 versus iron sucrose), and 14 RCTs of FCM (11 versus oral iron and 3 versus iron sucrose). In an ITC via iron sucrose, IIM resulted in a significantly larger increase from baseline hemoglobin with a mean difference of +0.249 g/dL with IIM relative to FCM, but there was no significant difference in the proportion of patients with a clinically-relevant response.

Conclusions: IIM resulted in a larger increase from baseline hemoglobin than FCM in patients with IDA, but with no difference in the proportion of patients responding. Studies comparing IIM and FCM directly would be needed to confirm these findings.

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KEYWORDS
Iron deficiency anemia; iron; administration; intravenous; indirect treatment comparison

1. Background and aims

Iron deficiency remains the leading cause of anemia globally [1]. Populations at high risk of iron deficiency anemia (IDA) include post-partum women, and those with chronic kidney disease (including patients on hemodialysis), inflammatory bowel disease (IBD), or gastrointestinal cancers.

The effectiveness of IDA treatment with oral iron is limited by gastrointestinal absorption and is particularly ineffective in the setting of coexisting acute or chronic medical conditions [2,3]. Oral iron is also associated with frequent gastrointestinal side effects, which can in turn result in poor adherence to treatment [4,5]. As such, intravenous (IV) iron has a well-established role in the treatment of IDA when oral iron is ineffective or cannot be used; for instance, IV iron is the recommended first-line therapy in patients with clinically active IBD, intolerance to oral iron or hemoglobin levels below 10 g/dL [6]. Blood transfusion represents another parenteral treatment option, but the higher risk of adverse outcomes with allogeneic red blood cell transfusion has increased the interest in the use of IV iron, particularly in acute clinical settings [2,7,8].

Although older IV iron formulations such as high molecular weight iron dextran were associated with risks of anaphylaxis, newer formulations such as iron isomaltoside (IIM; Monofer®, Pharmacosmos A/S, Holbæk, Denmark) and ferric carboxymaltose (FCM; Ferinject®, Vifor Pharma, Glattbrugg, Switzerland) have alleviated these concerns through increased stability and reduced levels of circulatory labile iron [2,9,10].

IIM is an IV iron product designed for rapid infusion, suitable for administration in primary care and other non-hospital settings [11]. IIM is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles, enabling a controlled and slow release of bioavailable iron to iron-binding proteins with low risk of free iron [11]. The structural characteristics of the complexing carbohydrate greatly reduce the risk of IIM inducing immune reactions *in vivo* [12]. These characteristics allow for flexible dosing, including high and rapid dosing (up to 20 mg per kilogram body weight) securing convenient IV iron therapy for a wide range of patients. FCM makes use of a different stabilizing carbohydrate shell from IIM, but has comparable administration requirements, albeit limited to a maximum of 1,000 mg per 15-minute infusion as compared to 20 mg/kg infusions with IIM.

The aim of the present study was to systematically search the literature to identify trials comparing IIM with FCM or, in the case where no data are available, to identify trials that would facilitate an indirect treatment comparison (ITC) of the efficacy of IIM and FCM in patients with IDA.

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Supplemental data for this article can be accessed here.

2. Methods

2.1. Databases and search strategy

An *a priori* literature search strategy was devised in which an initial systematic literature review would be conducted with the objective of identifying data from randomized controlled trials directly comparing IIM with FCM in the treatment of IDA. Should the initial review return no studies, additional searches would then be conducted to identify all RCTs of IIM, and all RCTs of FCM, with the aim of identifying potential pathways for an ITC of IIM with FCM via a common comparator. The search terms devised for each of the three searches included a combination of free-text, keyword, and Chemical Abstracts Service (CAS) Registry Number terms with the search terms covering study design terms, compound names, and terms pertaining to injections, infusions, and IV administration (Table 1). The MEDLINE, EMBASE, and Cochrane Library literature databases were searched, along with ClinicalTrials.gov, the International Clinical Trials Registry (ICTR) and the Australian New Zealand Trials Registry (ANZCTR).

2.2. Study selection

The titles and abstracts of all articles retrieved from the database and registry searches were screened by two independent researchers with the objective of identifying randomized controlled trials of IIM versus FCM (Search 1), IIM versus any other comparator (Search 2), or FCM versus any other comparator (Search 3) in patients with IDA. Exclusion criteria were applied to exclude studies that were not RCTs, did not include the correct intervention, were not conducted in the population of interest, or did not include the appropriate comparators (Table 2). Reviews or meta-analyses retrieved in the searches were excluded but were tagged as such and subsequently hand-searched for additional relevant trials.

2.3. Bias assessment

Included studies were assessed for potential biases in line using the criteria outlined in the Cochrane Risk of Bias Tool, covering random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting of outcomes (reporting bias) [13].

2.4. Meta-regression and indirect treatment comparison

The indirect comparison considered two patient-relevant efficacy measures: change in Hb level from baseline (in g/dL), and the proportion of patients achieving a clinically relevant response (defined in most studies of IDA as ≥2.0 g/dL from baseline). As both outcomes are dependent on several factors that vary between the studies (including baseline Hb, dose of IV iron, and time point of outcome measurement), a meta-regression feasibility assessment was conducted incorporating these factors

Table 1. Search terms for literature review.

Category	Description	Search terms[1]
Study design	Randomized controlled trials Systematic review and meta-analyses	random*; blind*; parallel*; placebo; crossover; assign*
Population	Iron deficiency anemia	Not limited in electronic searches; limited to IDA in screening of search results.
Search 1 – IIM vs FCM		
Intervention	Iron isomaltoside	Monofer OR 'ferric derisomaltose' OR 'iron isomaltooligosaccharide OR 'iron oligosaccharide' OR iron isomaltopentaoside OR iron isomaltoside OR 1345510-43-1.rn. OR AHU547PI9H.af. AND inject* OR infus* OR intravenous*
Comparator	Ferric carboxymaltose	'ferric carboxymaltose' OR Ferinject OR 'iron carboxymaltose' OR 9007-72-1.rn. OR 6897GXD6OE.af. AND inject* OR infus* OR intravenous*
Search 2 – Iron isomaltoside		
Intervention	Iron isomaltoside	As above
Comparator	Not limited	-
Search 3 – Ferric carboxymaltose		
Intervention	Ferric carboxymaltose	As above
Comparator	Not limited	-

Table 2. Exclusion criteria.

Reason for exclusion	Examples of excluded studies
(A) Not a randomized trial	Single arm studies, observational studies, dose-finding PK studies
(B) Incorrect intervention	Did not use intervention in alignment with Product Information/proposed use in an adult population with iron deficiency anemia.
(C) Does not include adult population with iron deficiency anemia	The intended use is for patients with IDA, requiring total iron replacement dosing. Intravenous iron is also used in populations without anemia, such as pre-surgery, chronic heart failure, restless legs syndrome. Trials of maintenance of Hb in HD CKD through regular small doses were also excluded.
(D) Not compared with main comparator	Search 1: comparators other than FCM Search 2: no limit; used to identify a potential network for ITC Search 3: based on the results of Search 2, limited to comparators of oral iron, or iron sucrose, to form a single-step network.

to establish if differences between the included studies were significant. Differences in the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and AEs of special interest (hypersensitivity and hypophosphatemia) were also included in the *a priori* ITC analysis plan.

During data extraction, steps were taken to maximize the consistency of study outcomes, specifically using outcomes adjusted for baseline Hb where available, using results presented at comparable time points (in addition to the primary time point for the studies), and grouping trials by IV iron dose category (up to 1000 mg IV iron; more than 1000 mg).

The ITC was conducted using the Bucher *et al*. method of adjusted indirect comparison, in which pooled effect estimates of differences between the comparators of interest (IIM and FCM) and a common comparator was combined in the ITC, thereby preserving the effects of randomization in the included studies [14]. Pooled effect estimates were derived using random effects models for both outcomes explored, employing the inverse variance method to combine intervention effect estimates for the continuous outcome of change from baseline hemoglobin [15], and the Mantel-Haenszel method to pool the dichotomous outcome of clinically relevant response [16].

2.5. Sensitivity analyses

To explore the effects of applying a minimal clinically important difference (MCID) to the ITC outcomes, non-inferiority margins of −0.5g/dL for change in hemoglobin, and −12.5% for the risk difference in the proportion of responders were applied in line with the non-inferiority margins utilized in RCTs of IV iron [17,18]. Furthermore, analyses were conducted in which studies differing in key trial characteristics (such as time to primary endpoint and definitions of clinically relevant response) were omitted.

3. Results

3.1. Systematic literature review

The literature search for RCTs comparing FCM and IIM returned five results, all of which were ongoing trials identified through ClinicalTrials.gov (Supplementary Table 1 and Supplementary Figure 1). The search for all RCTs of IIM identified 24 publications reporting outcomes from 5 different studies (Figure 1), while the search for all RCTs of FCM identified 47 publications reporting outcomes from 14 different studies (Figure 2). Of the 5 IIM trials, 4 were comparisons with oral iron [19], and 1 was a comparison with iron sucrose [20], and of the 14 FCM trials, 11 were comparisons with oral iron and 3 were comparisons with iron sucrose [21–23].

The searches also identified one published network meta-analysis including IIM, specifically comparing FCM, IIM, IS and oral iron in patients with IBD [24], incorporating the results of five RCTs. One other frequentist meta-analysis was identified that included a single study of IIM, but the IIM study did not contribute to the primary outcome due to lack of data availability, as the analysis was based on published data only [25]. Three other published meta-analyses were included in the searches, but did not include any studies of IIM, and did not include any studies of FCM that were not already captured by the present searches [26–28].

3.2. Common comparator and study selection

Based on the studies identified in the systematic literature review, two possible routes for an indirect comparison of IIM and FCM were identified: via oral iron or via iron sucrose (Figure 3). Of the studies comparing FCM with iron sucrose (n = 3), results from the two studies reporting the change from baseline hemoglobin exhibited low heterogeneity (I^2 = 0%), with a mean difference of +0.21 g/dL in favor of FCM, compared to a mean difference +0.46 g/dL in favor of IIM in the Derman *et al*. study comparing IIM with iron sucrose [20]. All three studies comparing FCM with iron sucrose reported the proportion of patients experiencing a clinically-relevant response, again exhibiting low heterogeneity (I^2 = 0%) with a risk difference of +8% in favor of FCM relative to iron sucrose, compared to +17% in favor of IIM in the Derman *et al*. study. Inadequate reporting and inconsistent definitions of TEAEs, serious TEAEs, and AEs of special interest (hypersensitivity and hypophosphatemia) precluded a formal indirect comparison of treatment safety via either oral iron or iron sucrose.

Heterogeneity was much higher in the oral iron network, with the IIM versus oral iron random effects analysis yielding an I^2 of 80% over the four studies included in the analysis of change from baseline hemoglobin, and the FCM versus oral iron analysis resulting in an I^2 of 74% over the 11 included studies. Heterogeneity was similarly high when pooling outcomes reporting the proportion of patients achieving clinically relevant response with FCM versus oral iron, with an I^2 of 87% (n = 10).

Important aspects of trial design, iron dosing, and hematological outcomes were also more consistent in the iron sucrose network than the oral iron network. Mean doses of IIM and FCM fell within the range of 1377 mg to 1640 mg in the iron sucrose network, compared with 849 mg to 1568 mg in the oral network, and the weighted average dose in the FCM group was notably higher than the IIM group (1253 mg versus 926 mg). Similarly, the proportions of patients achieving clinically relevant response varied from 3.7% to 94.1% in the trials included in the oral iron network but were (relatively) comparable within the iron sucrose trials (ranging from 41.0% to 65.5%). The single-step network via iron sucrose was therefore selected as the most robust method of comparison, with the most homogeneous trial designs and populations, and a reduced likelihood of violating the transitivity assumption.

The meta-regression feasibility study, examining the possibility of ascertaining the significance of baseline hemoglobin as a predictive factor for change from baseline Hb and proportion of patients achieving clinically relevant response, found that the small number of trials, coupled with a lack of detail on some factors in the published trials of FCM, precluded the analysis.

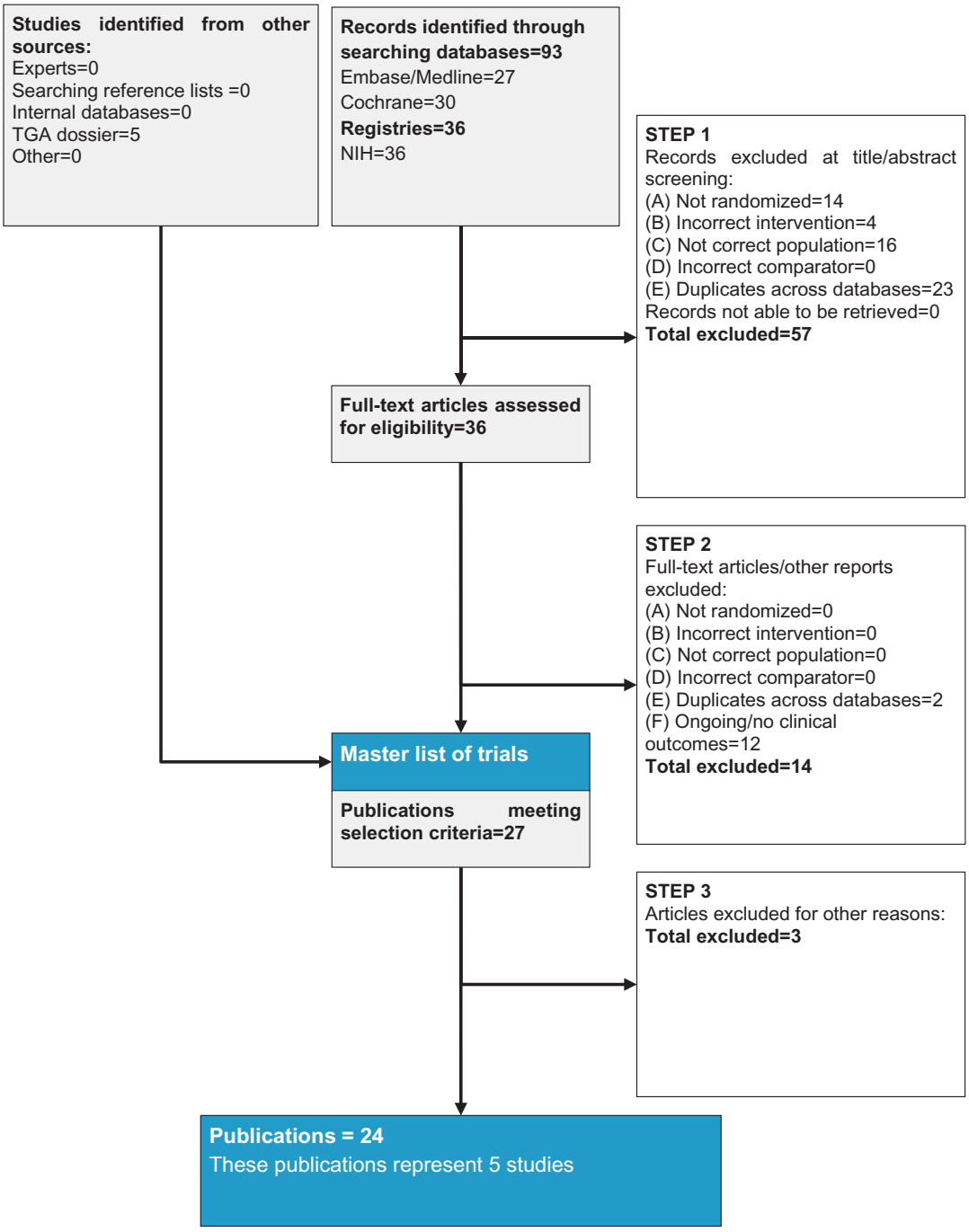

Figure 1. PRISMA flow diagram summary of searches for randomized controlled trials comparing iron isomaltoside any other comparator in patients with IDA.

3.3. Bias assessment and indirect treatment comparison

In the four RCTs in the iron sucrose network (Table 3) [20–23], the doses of IIM and FCM were comparable, with weighted average doses of 1640 mg and 1452 mg, respectively, and with the exception of one trial at 12 weeks [21], the primary time points for the other trials in the network were reasonably consistent with a range of 5–8 weeks. The bias assessment showed that no studies were at high risk of selection, performance, detection, attrition or reporting bias (Table 4).

The results of the ITC using the iron sucrose network showed significant improvements in the mean change from baseline hemoglobin outcomes with IIM relative to FCM. The mean difference in change in hemoglobin was 0.249 g/dL, with a 95% confidence interval (CI) of 0.072–0.426 g/dL. The risk difference of response was 0.085 (95% CI −0.013–0.183), corresponding to a non-significant difference of 8.5% (p = 0.0891) directionally in favor of IIM in the proportion of patients achieving a clinically relevant response.

In the sensitivity analysis in which an MCID was applied as a non-inferiority margin in line with many of the RCTs of iron replacement therapies (either oral or IV), the difference in change from baseline hemoglobin would be considered non-inferior. In the context of a 0.5 g/dL difference being the MCID, the mean change of 0.249 g/dL reported by the ITC would not be considered clinically relevant, a finding

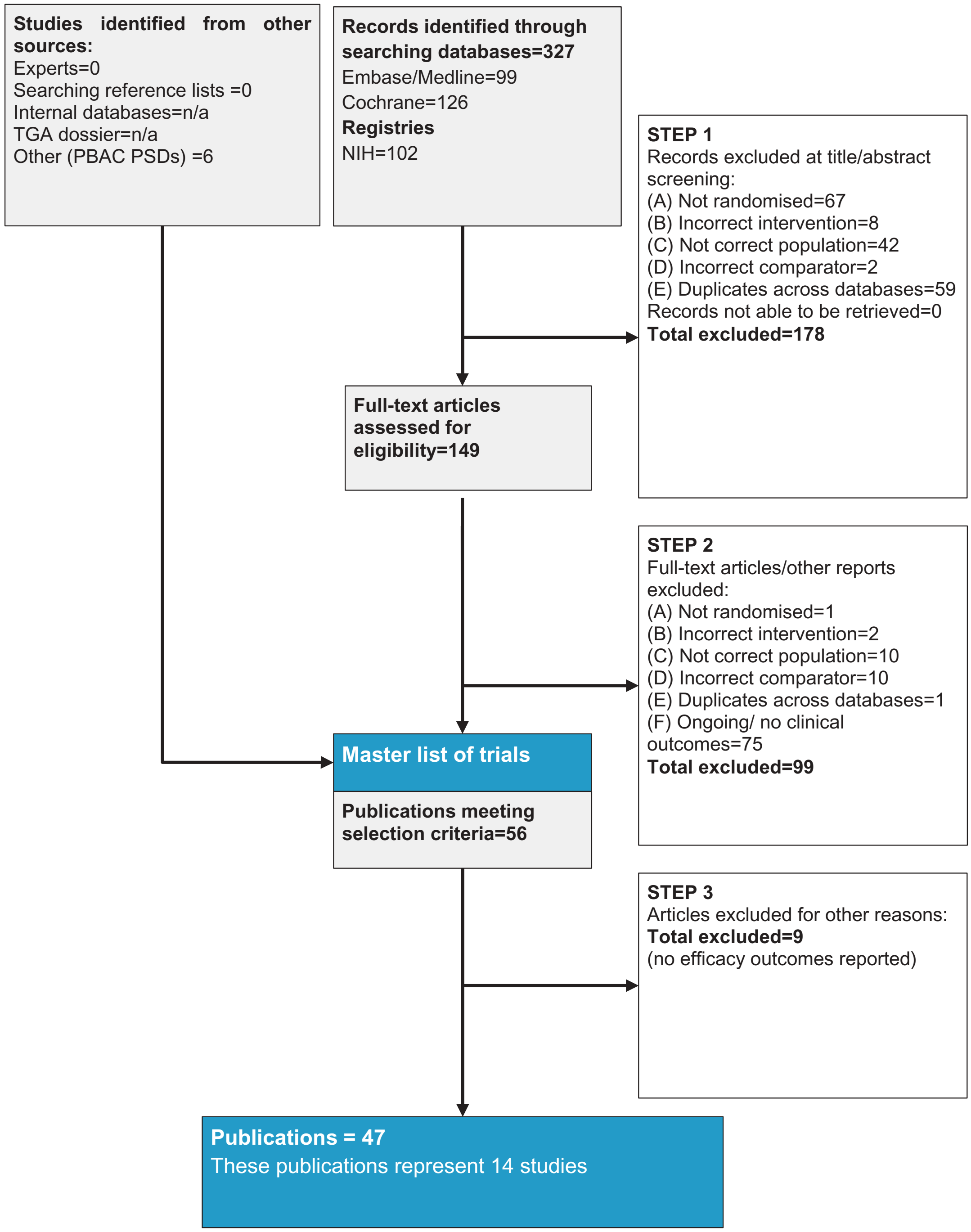
Studies identified from other sources:
Experts=0
Searching reference lists =0
Internal databases=n/a
TGA dossier=n/a
Other (PBAC PSDs) =6
Records identified through searching databases=327
Embase/Medline=99
Cochrane=126
Registries
NIH=102
STEP 1
Records excluded at title/abstract screening:
(A) Not randomised=67
(B) Incorrect intervention=8
(C) Not correct population=42
(D) Incorrect comparator=2
(E) Duplicates across databases=59
Records not able to be retrieved=0
Total excluded=178
Full-text articles assessed for eligibility=149
STEP 2
Full-text articles/other reports excluded:
(A) Not randomised=1
(B) Incorrect intervention=2
(C) Not correct population=10
(D) Incorrect comparator=10
(E) Duplicates across databases=1
(F) Ongoing/ no clinical outcomes=75
Total excluded=99
Master list of trials
Publications meeting selection criteria=56
STEP 3
Articles excluded for other reasons:
Total excluded=9
(no efficacy outcomes reported)
Publications = 47
These publications represent 14 studies

Figure 2. PRISMA flow diagram summary of searches for randomized controlled trials comparing ferric carboxymaltose with any other comparator in patients with IDA.

that would be consistent with the lack of significance in the outcome reporting the proportion of patients achieving a clinically-relevant response.

4. Discussion

This indirect comparison of IIM versus FCM in patients with IDA represents the first attempt to establish the relative efficacy of IIM and FCM across a population of patients with IDA either intolerant of oral iron or following the failure of oral iron treatment. The primary analysis showed a significant improvement in the mean change from baseline hemoglobin with IIM relative to FCM, but no significant difference in the proportion of patients experiencing a clinically relevant response.

The only previous meta-analysis including IIM in the primary outcome that was identified in the literature searches was the Aksan *et al*. network meta-analysis, which focused on comparing FCM, IIM, IS and oral iron in patients with IBD within a Bayesian framework [24]. Although the authors reported insignificant statistical heterogeneity across the 5 RCTs used in the network meta-analysis, the clinical outcomes, time horizon, and treatment dosing were not consistent across the studies [29]. Hematological inclusion criteria, and hence baseline Hb values varied widely, not all trials included patients with mild anemia and some trials did not

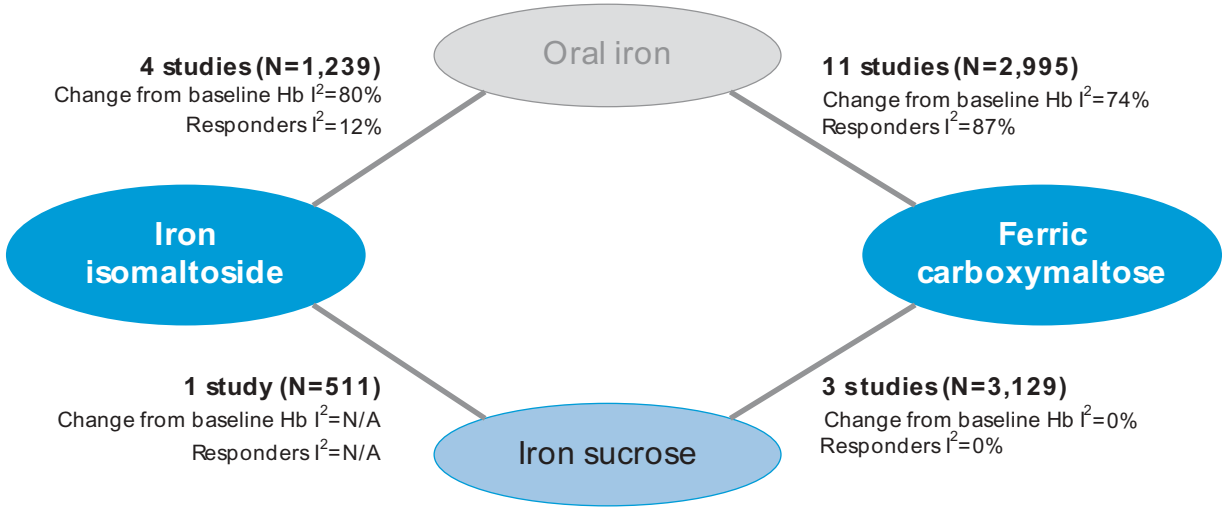

Figure 3. Network diagram showing the comparison anchors for an indirect comparison of iron isomaltoside with ferric carboxymaltose.
N/A, not applicable. The N values represent the total number of patients randomized to the relevant treatment arms across the included studies.

Table 3. Studies included in the iron sucrose indirect treatment comparison.

Trial	Population	Intervention	Comparator	Primary outcomes
Iron isomaltoside versus iron sucrose				
Derman *et al.* 2017 [20]	IDA multiple causes	IIM Simplified dosing schema	IS Ganzoni	Proportion of patients with hemoglobin increase ≥2 g/dL from baseline to any time between weeks 1–5.
Ferric carboxymaltose versus iron sucrose				
Evstatiev *et al.* 2011 [21]	IDA IBD	FCM Simplified dosing schema	IS Ganzoni	Proportion of patients with hemoglobin increase ≥2 g/dL from baseline to week 12.
Onken *et al.* 2014 [22]	IDA NDD-CKD	FCM 1500 mg (750 mg x 2)	IS 1000 mg (200 mg x 5)	Highest change in hemoglobin from baseline to day 56.
Mahey *et al.* 2016 [23]	IDA HUB (IUB)	FCM Ganzoni	IS Ganzoni	Change in hemoglobin from baseline to week 12.

FCM, ferric carboxymaltose; HUB, heavy uterine bleeding; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; IIM, iron isomaltoside; IS, iron sucrose; NDD-CKD, non-dialysis dependent chronic kidney disease

employ the standard definition of response (hemoglobin normalization or ≥2 g/dL increase) as the primary outcome. Despite the heterogeneity, the conclusion of the study was in agreement with the present study on the primary outcome of the proportion of patients achieving a hematological response, demonstrating no significant difference between IIM and FCM; change from baseline hemoglobin was not analyzed by Aksan *et al.*

The present study had certain limitations that should be considered when interpreting the findings. The most notable limitation was the small number of studies included in the analysis, with only one study identified to inform the relative efficacy of IIM and iron sucrose. While this may limit the generalizability of the findings, the included trials were relatively large, with a total of 511 patients enrolled in the trial comparing IIM with iron sucrose, and 3,129 patients enrolled in the trials comparing FCM with iron sucrose. Furthermore, the iron sucrose trials exhibited low levels of heterogeneity in both the analysis of change from baseline hemoglobin and the analysis of the proportion of patients achieving a clinically relevant response. This low heterogeneity was a key strength of the present analysis, particularly given the high degrees of heterogeneity noted in previous meta-analyses of IV iron [25,26].

A sensitivity analysis in which the MCID was taken into account showed that the improvement in the change from baseline hemoglobin would not be considered clinically important. If, on the basis of this comparison, the outcome of the ITC is interpreted as non-inferior, the focus on the choice of iron formulation shifts away from efficacy considerations and on to the safety of each formulation (including incidence of TEAEs and AEs of special interest such as hypersensitivity and hypophosphatemia), and economic and logistical factors.

While the quality of reporting and definitions of AEs employed in the studies identified precluded a formal indirect comparison of treatment safety in the present analysis, Kalra and Bhandari published an analysis of anaphylactic reaction incidence in patients with IDA treated with IIM, FCM or iron sucrose. The authors identified adverse events using an established Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) for anaphylaxis, covering hypersensitivity, allergic reactions, and any serious or severe treatment-emergent adverse event occurring on the day of or the day after dosing. Applying the anaphylaxis SMQ to data from 5,007 IDA patients (1,729 patients using IIM, 1,775 patients using FCM, and 1,503 patient using iron sucrose) showed a significantly lower incidence of anaphylactic reactions in patients

Table 4. Information required to assess the risk of bias in randomized trials.

Trial	Assessment
Selection bias (random sequence generation and allocation concealment)	
Derman *et al.* 2017 [20]	Statistician prepared randomization lists using eCRF software, IWRS for allocation.
Evstatiev *et al.* 2011 [21]	Predefined, computer-generated list. Sequentially numbered randomization envelopes provided by a third party.
Onken *et al.* 2014 [22]	The randomization schedule was generated prior to study start and the treatment group was assigned using an interactive voice-response system.
Mahey *et al.* 2016 [23]	Computerized randomization table.
Performance bias (blinding of participants and personnel)	
Derman *et al.* 2017 [20]	No
Evstatiev *et al.* 2011 [21]	No
Onken *et al.* 2014 [22]	No
Mahey *et al.* 2016 [23]	No
Detection bias (blinding of outcome assessment)	
Derman *et al.* 2017 [20]	The outcome measures were based on laboratory results.
Evstatiev *et al.* 2011 [21]	The outcome measures were based on laboratory results.
Onken *et al.* 2014 [22]	The outcome measures were based on laboratory results.
Mahey *et al.* 2016 [23]	The outcome measures were based on laboratory results.
Attrition bias (incomplete outcome data)	
Derman *et al.* 2017 [20]	Descriptive statistics and statistical analyses were performed using observed cases, i.e. no imputation of missing data was performed.
Evstatiev *et al.* 2011 [21]	Missing data were treated as missing, and only observed cases were used for analysis.
Onken *et al.* 2014 [22]	NR
Mahey *et al.* 2016 [23]	NR
Reporting bias (selective reporting of outcomes)	
Derman *et al.* 2017 [20]	Primary and key secondary outcomes all reported.
Evstatiev *et al.* 2011 [21]	Primary and key secondary outcomes all reported.
Onken *et al.* 2014 [22]	Primary and key secondary outcomes all reported.
Mahey *et al.* 2016 [23]	Primary and key secondary outcomes all reported.

eCRF, electronic case report form; IWRS, interactive web response system; NR, not reported

using IIM (0.6%) relative to FCM (1.5%, p = 0.011) and iron sucrose (1.6%, p = 0.005) [30]. Recent data from a head-to-head randomized study in normophosphatemic women with gynecological bleeding have also shown a significantly lower incidence of hypophosphatemia with IIM relative to FCM. Over 28 days after a single IV injection of equivalent doses of FCM and IIM, 9 out of 12 patients with FCM had experienced hypophosphatemia (plasma phosphorus <2.0 mg/dl) relative to 1 out of 13 with IIM (p = 0.001) [31].

Economic and logistic differences between formulations may include, for example, the costs borne by health-care payers in purchasing each iron formulation, the number of infusions required to correct the iron deficiency with each formulation, and any differences in the infusion procedure that may require additional time from a health-care professional. Two studies have been published exploring the resource use and budget implications of using IIM relative to FCM, concluding that the 20 mg/kg infusion with IIM would reduce the number of infusions required for iron correction from 1.8 with FCM to 1.3 with IIM in a general IDA population, and from 1.6 with FCM to 1.2 with IIM in a population with IBD [32,33]. Based on these data, the safety and economic profile of IIM would appear to be favorable relative to FCM.

5. Conclusion

The present study demonstrated that IIM resulted in a statistically significant improvement in the change from baseline hemoglobin relative to FCM via a common comparator of iron sucrose in patients with IDA. Direct studies comparing the two IV iron formulations would be required to definitely conclude whether there is a meaningful difference in efficacy. Five such studies were identified in the present study that are ongoing and the question of the relative efficacy of FCM and IIM should be revisited when the results are reported. Meanwhile, decisions regarding which iron formulation should be used to treat patients with IDA either intolerant or unresponsive to oral iron can be made without concerns around substantial differences in efficacy.

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Author's contributions

G Muduma conceived of the study; G Muduma and RF Pollock were involved in the design, analysis, and interpretation of data; RF Pollock drafted the paper; and G Muduma revised it critically for intellectual content. G Muduma and RF Pollock approve of the final version to be published and both authors agree to be accountable for all aspects of the work.

Declaration of interest

RF Pollock is a shareholder and director of Covalence Research Ltd, which received consultancy fees from Pharmacosmos A/S for the present study. G Muduma is a full-time employee of Pharmacosmos A/S, the marketing authorization holder for iron isomaltoside (Monofer). The study and medical writing activities were funded wholly by Pharmacosmos A/S. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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