

Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory Bowel Disease

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Stefanos Bonovas, MD, MSc, PhD, Gionata Fiorino, MD, PhD, Mariangela Allocca, MD, PhD, Theodore Lytras, MD, MPH, Argirios Tsantes, MD, PhD, Laurent Peyrin-Biroulet, MD, PhD, and Silvio Danese, MD, PhD

Abstract: Anemia is the most prevalent extraintestinal complication of inflammatory bowel disease (IBD). Our aim was to evaluate the comparative efficacy and harm of intravenous (IV) versus oral iron supplementation for correcting anemia in adult IBD patients.

We conducted a systematic review and meta-analysis to integrate evidence from randomized controlled trials having enrolled adults with IBD, and comparing IV versus oral iron (head-to-head) for correcting

iron-deficiency anemia. Medline, Embase, Scopus, and the Web of Science database were searched through July 2015. The Cochrane Central Register of Controlled Trials, the WHO International Clinical Trials Registry Platform, the ClinicalTrials.gov, and international conference proceedings were also investigated. Two reviewers independently abstracted study data and outcomes, and rated each trial's risk-of-bias. Pooled odds ratio (OR) estimates with their 95% CIs were calculated using fixed- and random-effects models.

Five eligible studies, including 694 IBD patients, were identified. In meta-analysis, IV iron demonstrated a higher efficacy in achieving a hemoglobin rise of ≥ 2.0 g/dL as compared to oral iron (OR: 1.57, 95% CI: 1.13, 2.18). Treatment discontinuation rates, due to adverse events or intolerance, were lower in the IV iron groups (OR: 0.27, 95% CI: 0.13, 0.59). Similarly, the occurrence of gastrointestinal adverse events was consistently lower in the IV iron groups. On the contrary, serious adverse events (SAEs) were more frequently reported among patients receiving IV iron preparations (OR: 4.57, 95% CI: 1.11, 18.8); however, the majority of the reported SAEs were judged as unrelated or unlikely to be related to the study medication. We found no evidence of publication bias, or between-study heterogeneity, across all analyses. Risk of bias was high across primary studies, because patients and personnel were not blinded to the intervention.

IV iron appears to be more effective and better tolerated than oral iron for the treatment of IBD-associated anemia.

(*Medicine* 95(2):e2308)

Abbreviations: CD = Crohn's disease, CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, IBD = inflammatory bowel disease, IV = intravenous, OR = odds ratio, PRISMA = preferred reporting items for systematic reviews and meta-analyses, PROSPERO = international prospective register of systematic reviews, RCT = randomized controlled trial, RoB = risk of bias, SAE = serious adverse event, UC = ulcerative colitis.

INTRODUCTION

Anemia is considered the most frequent extraintestinal manifestation of inflammatory bowel disease (IBD), usually complicating the course both in ulcerative colitis (UC) and Crohn disease (CD).^{1,2} It is detected in up to 20% of outpatients and 70% of hospitalized patients with IBD.³⁻⁵ In the majority of cases, IBD-associated anemia represents a combination of chronic iron deficiency and anemia of chronic disease.^{6,7} Other less frequent causes include vitamin B₁₂ and folate deficiency, and toxic effects of medications.^{8,9} At the patient level, anemia significantly impairs quality of life, and the physical, emotional, and cognitive functions,¹⁰ while at an economic level, it increases the risk of hospitalization and surgery, as well as healthcare costs.¹¹

Editor: Fadi Mourad.

Received: October 22, 2015; revised: November 18, 2015; accepted: November 22, 2015.

From the IBD Center, Department of Gastroenterology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy (SB, GF, MA, SD); Humanitas University, Rozzano, Milan, Italy (SD); Department of Experimental and Health Sciences, Pompeu Fabra University, Barcelona, Spain (TL); Centre for Research in Environmental Epidemiology, Barcelona, Spain (TL); Hellenic Center for Disease Control and Prevention, Athens, Greece (TL); Laboratory of Hematology and Blood Bank Unit, "Attikon" University Hospital, School of Medicine, University of Athens, Athens, Greece (AT); and Department of Hepato-Gastroenterology and Inserm U954, University Hospital of Nancy, Lorraine University, Vandoeuvre-lès-Nancy, France (LP-B).

Correspondence: Stefanos Bonovas, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano, Milan, Italy (e-mail: sbonovas@gmail.com and stefanos.bonovas@humanitasresearch.it).

Supplemental Digital Content is available for this article.

Systematic review registration number: PROSPERO 2015; CRD42015024697.

Conception and design: all authors; obtaining funding: SD; literature search and data collection: all authors; statistical analysis: TL and SB; data interpretation: all authors; drafting of the manuscript: SB; critical revision of the manuscript for important intellectual content: all authors; final approval of the version to be published: all authors.

This study was funded by the Centro Ricerca e Cura delle Malattie Infiammatorie Croniche Intestinali, Istituto Clinico Humanitas. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

GF has served as a consultant and advisory board member for MSD, Takeda, AbbVie, and Janssen. LP-B has received consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilege, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, Pfizer, and HAC-pharma, and lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellex, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson.

All other authors have no conflicts of interest to disclose.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002308

Iron supplementation is recommended in all IBD patients when iron-deficiency anemia is present.⁸ This can be undertaken using oral or intravenous (IV) iron preparations. Oral iron is convenient and inexpensive, but its efficacy is limited by poor absorption, intolerance, and frequent adverse effects. IV iron is better tolerated; however, the costs associated with IV iron administration might limit its widespread use.¹² The recent European Crohn's and Colitis Organization (ECCO) guidelines⁸ conclude that "IV iron is more effective, shows a faster response, and is better tolerated than oral iron" and state that "IV iron should be considered as first line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 10.0 g/dL, and in patients who need erythropoiesis-stimulating agents; while oral iron may be used in patients with mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron."⁸

Nevertheless, there is still much controversy about whether iron should be supplemented orally or intravenously, with a great number of physicians still being uncertain as to which treatment modality they should select for their patients.¹³ This uncertainty has been amplified by a very recent meta-analysis that found no statistically significant difference between IV and oral iron in correcting iron-deficiency anemia in IBD.¹⁴ However, we have spotted important data extraction errors in that study (see Appendix, <http://links.lww.com/MD/A611>) raising serious doubts about the validity of reported conclusions. As a result, we decided it was important to start afresh; thus our objective was to conduct a new systematic review and meta-analysis of published trials assessing and comparing the efficacy and harm of IV versus oral iron supplementation for correcting iron-deficiency anemia in patients with IBD, and to provide a useful evidence summary to support clinical decision making.

METHODS

Protocol and Registration

Our study protocol¹⁵ is registered with the International Prospective Register of Systematic Reviews (PROSPERO, <http://www.crd.york.ac.uk/prospéro>). The current systematic review and meta-analysis was performed adhering to the guidelines established by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement.¹⁶

The study did not involve any experiment on humans or animals, thus an ethical approval was not necessary.

Data Sources and Search Strategy

A systematic search of Medline, Embase, Scopus, and the Web of Science database was conducted from the date of inception of each database to July 20, 2015. Search terms included: crohn's disease, ulcerative colitis, or inflammatory bowel disease, combined with iron, ferric, ferrous, or anemia. The search was limited to clinical trials and humans. No language restrictions were imposed.

We also searched the Cochrane Central Register of Controlled Trials, the Cochrane Inflammatory Bowel Disease Group Specialized Trials Register, the WHO International Clinical Trials Registry Platform, and the ClinicalTrials.gov website for completed but unpublished studies; and recent international conference proceedings (European Crohn's and Colitis Organisation, 2011–2015; Digestive Disease Week, 2010–2015; and the United European Gastroenterology Week, 2010–2014). Two investigators independently examined the search results

and screened the titles and abstracts to exclude any reports that were clearly irrelevant. The full text of the remaining articles was critically assessed for eligibility, and their reference lists (as well as of relevant reviews and meta-analyses) were inspected to identify further eligible studies. We also asked field experts to provide additional evidences.

Study Selection and Data Extraction

In this meta-analysis, we considered randomized controlled trials (RCTs) with either a parallel or crossover design, having enrolled adult patients with IBD, and comparing IV versus oral iron supplementation against each other (ie, head-to-head trials) for correcting anemia. We accepted any definition of anemia used by study authors, provided that all male participants had <13.0 g/dL and all the female participants had <12.0 g/dL of hemoglobin (ie, all participants met the WHO criteria for anemia for adult males and nonpregnant females¹⁷). However, we are aware that some potential participants who met the WHO criteria may have not been enrolled in a trial because it used a different level of hemoglobin to diagnose anemia (eg, 11.0 g/dL of hemoglobin).

Studies were excluded if they were observational; did not investigate patients with IBD; did not report (or provided insufficient data for) the outcomes of interest; or were conducted in pediatric populations.

Our primary (efficacy) outcome was the effect of treatments on the hemoglobin response, defined as the rate of patients who achieved an increase of at least 2.0 g/dL in hemoglobin concentration at the end of the follow-up.

As secondary (safety) outcomes we studied: the rates of discontinuation of the intervention due to adverse events or intolerance; the occurrence of serious adverse events (SAEs), which are defined as any untoward medical occurrence that results in death, requires hospital admission or prolongation of existing hospital stay, causes persistent or significant disability/incapacity, or is life threatening¹⁸; and the rates of gastrointestinal adverse events (nausea, vomiting, abdominal pain, and diarrhea).

Data extraction was undertaken by 2 independent reviewers. Any discrepancy was resolved by consensus, referring back to the original article. The following data were extracted from each study: first author's name, journal and year of publication, study design and duration, number of participants, disease (eg, UC, CD), patient characteristics (age, concomitant treatments, duration of disease), details of iron supplementation, including dose, route, frequency, and duration, and rates of participants with events (ie, primary and secondary outcomes) reported for the IV and the oral iron groups.

Assessment of Risk of Bias

We evaluated the risk of bias (RoB) in included studies using the Cochrane Collaboration's tool,^{19,20} which addresses the following key domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias (eg, extreme baseline imbalances in prognostic factors, differential distributions of IBD type, etc.). These items were considered for the RoB assessment and were classified as "adequate" (low RoB), "inadequate" (high RoB), or "unclear" (uncertain RoB). Studies with adequate procedures in all domains were considered to have a low RoB; ones with inadequate procedures in 1 or more domains were

considered to have a high RoB; and those with unclear procedures in 1 or more domains were considered to have unclear RoB. Discrepancies among reviewers were discussed, and agreement was reached by consensus.

Data Synthesis and Analysis

The odds ratio (OR) was the metric of choice in all comparisons. Study-level ORs and their 95% CIs were calculated in accordance with the intention-to-treat principle: analysis was based on the total number of randomly assigned participants, irrespective of how the original study investigators analyzed the data. All drop-outs were treated as treatment failures (ie, failure to achieve an increase of at least 2.0 g/dL in hemoglobin concentration).

When no events occurred in 1 group of the trial, we used a continuity correction that was inversely proportional to the relative size of the opposite group. In particular, the continuity correction for the IV iron group was $1/(R+1)$, where R is the ratio of oral iron group to IV iron group sizes. Similarly, the continuity correction for the oral iron group was $R/(R+1)$. This methodological approach outperforms the use of a constant continuity correction of 0.5 in a setting of sparse data and imbalanced study groups.²¹ Trials reporting zero-event data for both study groups were excluded from the analyses.

We used 2 techniques to calculate the pooled relative effect estimates: the fixed-effects model (Mantel-Haenszel approach),²² and the random-effects model (DerSimonian and Laird approach).²³ In the absence of heterogeneity, the fixed- and the random-effects model provide very similar results. When heterogeneity is found, the random-effects model might be more prudent, though both techniques may be biased.

To examine the stability of the results, we also performed a “leave-one-out” sensitivity analysis.²⁴ The scope of this approach was to evaluate the influence of individual studies, by calculating the summary effect estimate in the absence of each study.

Selective outcome reporting or publication bias was assessed using the Begg’s adjusted rank correlation test,²⁵ and the Egger’s regression asymmetry test.²⁶ The between-study heterogeneity was evaluated using the Cochran’s Q test,²⁷ with a 0.10 level of significance, and the I² statistic,^{28,29} which describes the percentage variation across studies that is due to heterogeneity rather than chance. Negative values of I² were put equal to zero, so that it lies between 0% and 100%. An I² value <40% was considered as indicative of “not important heterogeneity” and a value over 75% as indicative of “considerable heterogeneity.”³⁰

The quality of the meta-analytic evidence, for each of the outcomes, was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation).^{31,32}

For all analyses, we used the R software environment,³³ version 3.1.1, and the “meta” package for R,³⁴ version 4.2-0. All P values are 2-tailed. For all statistical tests (except for heterogeneity), a P value <0.05 was regarded as statistically significant.

RESULTS

Search Results

A summary of the literature search and selection process is presented in Figure 1 (Flow Diagram). Five RCTs^{35–39} comparing IV versus oral iron (head-to-head) for correcting iron-deficiency anemia in IBD patients met the eligibility criteria and were further analyzed.

Iron sucrose was the most frequent IV iron preparation used in the included trials,^{35,37,39} followed by iron isomaltoside,³⁸ and ferric carboxymaltose.³⁶ On the other hand, oral iron sulfate was used in 4 studies,^{36–39} and oral ferrous fumarate in 1.³⁵ The number of randomized participants varied between 19 and 338 in the included studies, and the follow-up times from 2 to 20 weeks. Imbalance was observed between the group sizes within studies (ratio, 1:1 or 2:1). The publication dates ranged

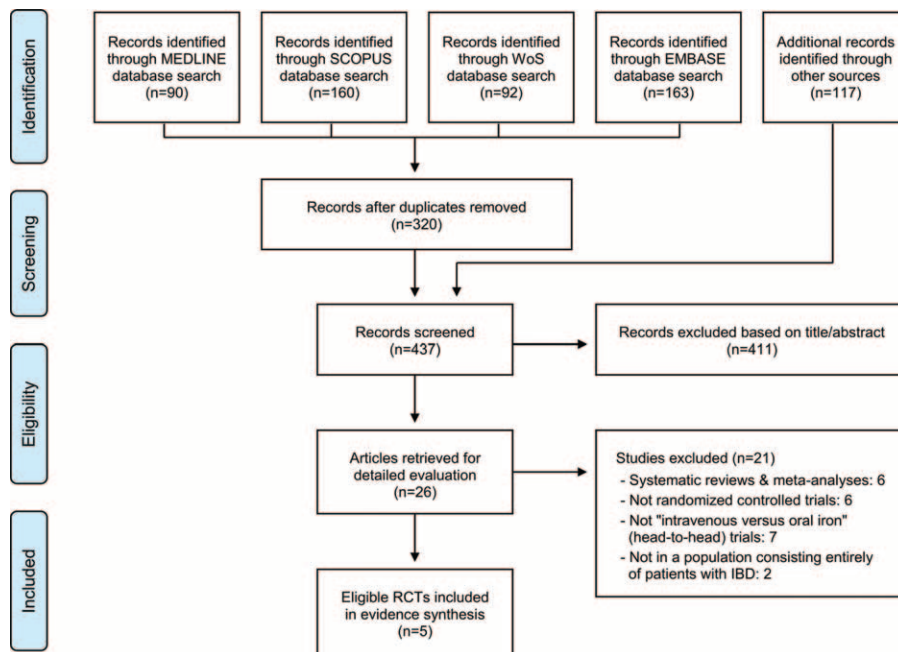


FIGURE 1. Summary of the evidence search and selection process. IBD = inflammatory bowel disease, RCTs = randomized controlled trials.

TABLE 1. Characteristics of the Randomized Controlled Trials Included in the Meta-Analysis

Study	Design	Route, Drug, and Dosage	Patients Randomized and Disease Activity	Hematological Inclusion Criteria: TSAT; Ferritin; Hb (♀/♂)	Hb at Enrollment	Age, y	Follow-Up, wk
Erichsen et al ³⁵	Crossover	IV iron sucrose 200 mg, 3 times over 2 wk Oral ferrous fumarate, 120 mg/d, 2 wk	19 IBD patients with quiescent and active disease	NS; <50 ng/mL; <12.0/13.0 g/dL	Mean: 11.1 g/dL	Range: 18–46	2
Kulnigg et al ³⁶	Parallel	IV iron carboxymaltose of up to 1000 mg, once every 4 wk, 12 wk Oral iron sulfate, 200 mg/d, 12 wk	200 IBD patients with mild-to-moderately active disease	<20%; <100 ng/mL; ≤11.0 g/dL	Median: 8.8 g/dL	Median: 42	12
Lindgren et al ³⁷	Parallel	IV iron sucrose 200 mg, once every 1–2 wk, 20 wk Oral iron sulfate, 400 mg/d, 20 wk	91 IBD patients at a modest disease activity	NS; <300 ng/mL; <11.5 g/dL	Mean: 10.4 g/dL	Mean: 42	20
Reimisch et al ³⁸	Parallel	IV iron isomaltoside of up to 1000 mg, once weekly, 8 wk Oral iron sulfate, 200 mg/d, 8 wk	338 IBD patients in clinical remission or with mild disease	<20%; NS; <12.0 g/dL	Median: 9.9 g/dL	Median: 36	8
Schröder et al ³⁹	Parallel	IV iron sucrose in a single dose of 7 mg/kg followed by five 200 mg doses, 5 wk Oral iron sulfate, 100–200 mg/d, 5 wk	46 IBD patients with quiescent and active disease	<20%; <20 ng/mL; <10.5/11.0 g/dL	Mean: 9.7 g/dL	Median: 34	6

Hb = hemoglobin, IBD = inflammatory bowel disease, IV = intravenous, NS = not specified, TSAT = transferrin saturation.

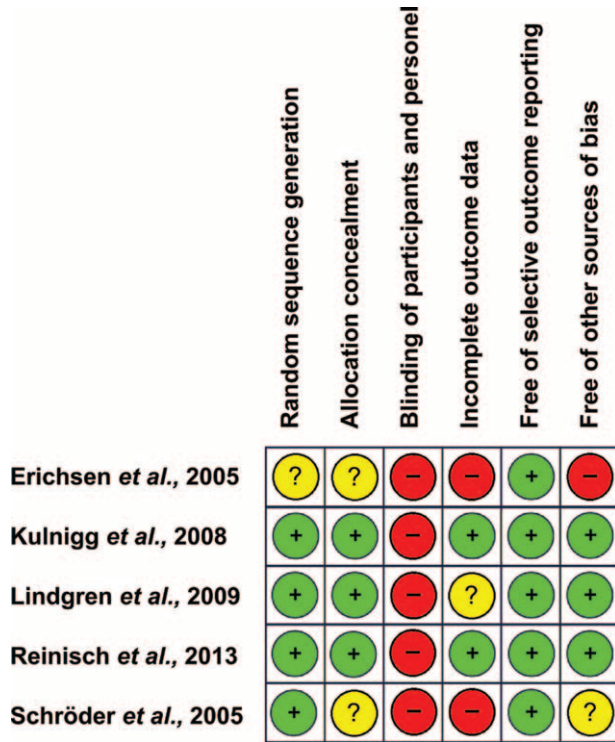


FIGURE 2. Risk-of-bias assessment for the randomized trials included in the meta-analysis. Symbols: green (+), low risk of bias; yellow (?), unclear risk of bias; red (-), high risk of bias.

between 2005 and 2013. A summary of the trials’ characteristics is given in Table 1.

Risk of Bias in Included Studies

Assessment of the RCTs, by use of the Cochrane Collaboration’s tool, revealed high RoB across the 5 studies.^{35–39} Participants and personnel were not blinded to the interventions. We are aware that it is impossible to blind trials comparing oral iron with IV, as oral iron is indicated by black stools; however, open-label design represents a major weakness, as it can bias the results by affecting either the actual patient outcomes (eg, differential drop-outs) or the outcomes’ assessment (considering how subjective the evaluation of gastrointestinal adverse events or iron intolerance may be). For this reason, we considered the whole group of trials to have a high RoB with regard to the “blinding of participants and personnel” domain. Quality assessment items are summarized in Figure 2.

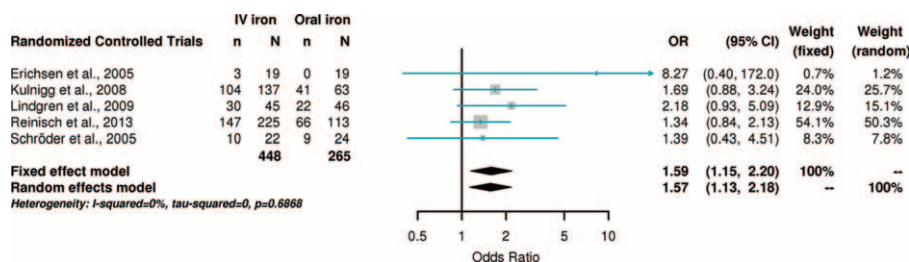


FIGURE 3. Forest plot for hemoglobin response (ie, increase of ≥ 2.0 g/dL): results from individual studies and meta-analysis. CI = confidence interval, IV = intravenous, OR = odds ratio.

Results of Meta-Analyses

Hemoglobin Increase ≥ 2.0 g/dL (Primary Outcome)

Five RCTs contributed to this analysis.^{35–39} Each trial reported a higher percentage of responders (defined as the proportion of patients with a hemoglobin increase of ≥ 2.0 g/dL) in the IV iron group as compared to the oral iron group. The overall response rate, on all 5 RCTs, was 65.6% in the IV iron groups, and 52.1% in the oral iron groups.

In meta-analysis, IV iron demonstrated a higher efficacy in achieving a hemoglobin rise of ≥ 2.0 g/dL in comparison to oral iron. The pooled effect estimate was statistically significant under both a fixed-effects (OR: 1.59, 95% CI: 1.15, 2.20) and a random-effects model (OR: 1.57, 95% CI: 1.13, 2.18). The ORs with their 95% CIs for the individual studies, and the pooled results, are presented in a forest plot (Figure 3). The Cochran’s Q test had a P value of 0.69 and the corresponding I² statistic was 0%, both indicating very little variability between the studies, although these statistical tests may be subject to type II error (lack of power to detect heterogeneity) given the small number of studies. The P values for the tests of Begg’s and Egger’s were P = 0.22 and P = 0.12, respectively, suggesting a low probability of publication bias (Table 2). The “leave-one-out” sensitivity analysis, removing 1 study at a time, confirmed the robustness of our results (Figure 4).

Treatment Discontinuation due to Adverse Events or Intolerance

Treatment discontinuation rate was lower in the IV iron groups (2.5%) as compared to the oral iron groups (10.9%). The summary effect estimate was statistically significant, either assuming a fixed-effects (OR: 0.24, 95% CI: 0.12, 0.49) or a random-effects model (OR: 0.27, 95% CI: 0.13, 0.59; Table 2). Results from the primary studies, and meta-analysis, are shown in Figure 5. Again, we found no evidence of publication bias (Begg’s, P = 0.99; Egger’s, P = 0.13) or heterogeneity (Cochran’s Q test, P = 0.42; I² = 0%) among the primary studies.

It is important to note, here, that the selection criteria applied in 3 studies,^{36,38,39} excluding patients with known intolerance to oral iron, may have caused a selection bias toward a favorable tolerability for oral iron in these studies, and thus, a bias toward the null (no difference) for the “treatment discontinuation” outcome in our meta-analysis. Hence, in unselected IBD populations, the tolerability to oral iron may be lower, and treatment discontinuation rates even higher (than 10.9%).

TABLE 2. Meta-Analysis Results

Outcome	No. of RCTs	Fixed-Effects Model	Random-Effects Model	Tests of Homogeneity			Tests of Publication Bias	
		OR (95% CI)	OR (95% CI)	Q Value (df)	P Value	I ² , %	Begg's P Value	Egger's P Value
Hemoglobin increase ≥2 g/dL	5	1.59 (1.15, 2.20)	1.57 (1.13, 2.18)	2.27 (4)	0.69	0	0.22	0.12
Discontinuation of the treatment due to adverse events or intolerance	5	0.24 (0.12, 0.49)	0.27 (0.13, 0.59)	3.87 (4)	0.42	0	0.99	0.13
Serious adverse events	4	5.45 (1.35, 22.0)	4.57 (1.11, 18.8)	0.61 (3)	0.90	0	0.99	0.64
Gastrointestinal adverse events								
Nausea	4	0.40 (0.15, 1.05)	0.43 (0.16, 1.17)	1.08 (3)	0.78	0	0.73	0.73
Vomiting	3	0.27 (0.07, 1.00)	0.28 (0.07, 1.07)	0.36 (2)	0.83	0	0.30	0.26
Abdominal pain	5	0.22 (0.09, 0.53)	0.28 (0.07, 1.16)	6.33 (4)	0.18	37	0.46	0.11
Diarrhea	5	0.15 (0.06, 0.39)	0.18 (0.07, 0.50)	2.20 (4)	0.70	0	0.99	0.13

CI = confidence interval, df = degrees of freedom, OR = odds ratio, RCTs = randomized controlled trials.

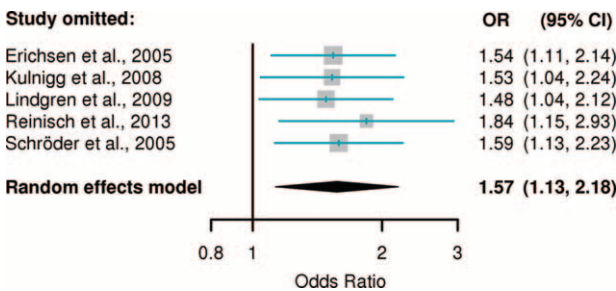


FIGURE 4. “Leave-one-out” sensitivity analysis for hemoglobin response (ie, increase of ≥2.0 g/dL): pooled estimates are from random-effects models, with 1 study omitted at a time. CI = confidence interval, OR = odds ratio.

Serious Adverse Events

The occurrence of SAEs was 4.2% in the IV iron groups (19 events), while only 1 was reported in the oral iron groups (0.4%). Continuity corrections, inversely proportional to the relative size of the opposite arm, were used in the analysis. Exposure to IV iron was associated with a significant increase in the risk of SAEs (fixed-effects model, OR: 5.45, 95% CI: 1.35, 22.0; and random-effects model, OR: 4.57, 95% CI: 1.11, 18.8). The ORs with their 95% CIs from the primary trials, and the pooled results, are presented in Figure 6. We found no evidence

of publication bias (Begg’s, *P* = 0.99; Egger’s, *P* = 0.64) or heterogeneity (Cochran’s Q test, *P* = 0.90; *I*² = 0%) among the studies (Table 2).

At this point, we should note that no cases of anaphylactic shock reactions were reported, and that the vast majority of the reported SAEs (18 of 20) were considered by the Safety Boards as unrelated, or unlikely to be related, to the study medications.

Gastrointestinal Adverse Events

The occurrence of gastrointestinal adverse events was consistently lower in the IV iron groups in comparison to the oral iron groups (nausea: 1.6% vs 4.9%, vomiting: 1.0% vs 6.8%, abdominal pain: 1.3% vs 7.9%, and diarrhea: 0.9% vs 8.3%). The fixed-effects summary estimates were statistically significant for abdominal pain (OR: 0.22, 95% CI: 0.09, 0.53) and diarrhea (OR: 0.15, 95% CI: 0.06, 0.39), but not for nausea (OR: 0.40, 95% CI: 0.15, 1.05) and vomiting (OR: 0.27, 95% CI: 0.07, 1.00). In each analysis, we found no evidence of publication bias or heterogeneity between studies (Table 2).

Quality of the Evidence

In this meta-analysis, the quality of synthesized evidence is judged as “moderate” for the following reasons:

- (i) the data were derived from RCTs (randomized study design is considered the gold standard for assessing therapeutic interventions),⁴⁰

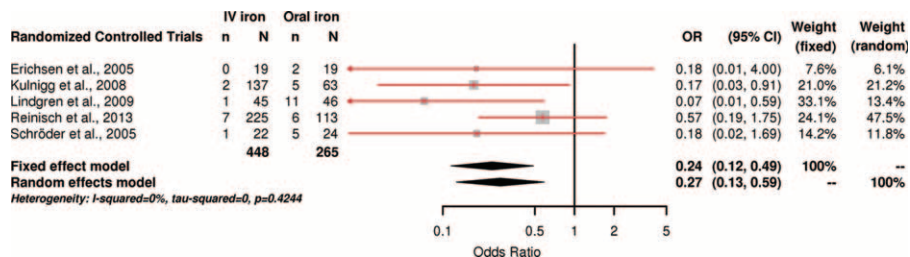


FIGURE 5. Forest plot for treatment discontinuation, due to adverse events or intolerance: results from individual studies and meta-analysis. CI = confidence interval, IV = intravenous, OR = odds ratio.

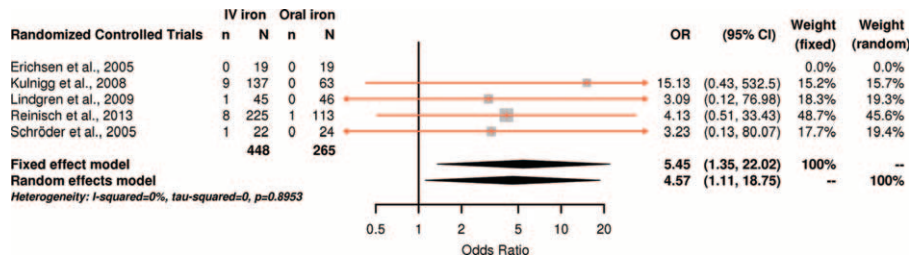


FIGURE 6. Forest plot for serious adverse events: results from individual studies and meta-analysis. CI=confidence interval, IV=intravenous, OR=odds ratio.

- (ii) the meta-analytic effect estimates are relatively precise (except for SAEs),
- (iii) the results are consistent (heterogeneity was not important across studies), and
- (iv) all the RCTs included in the meta-analysis are characterized by high RoB, because patients and personnel were not blinded to the intervention (a fact that downgrades the quality of evidence).

A “moderate” certainty of associations means that “we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.”³²

Using the GRADE system, a summary of findings and strength of evidence is shown in Table 3.

DISCUSSION

Anemia is the most prevalent extraintestinal complication of IBD and needs appropriate therapeutic approach. The aim of treatment is to supply enough iron to normalize hemoglobin concentrations and replenish iron stores, and thereby to improve quality of life, symptoms, and disease prognosis.⁴¹ Although iron supplementation is recommended in all IBD patients diagnosed with iron-deficiency anemia, a large number of physicians are uncertain as to which treatment modality they should select.¹³

In this systematic review and meta-analysis, we incorporated 5 RCTs comparing IV versus oral iron supplementation (head-to-head trials) for correcting iron-deficiency anemia in adult patients with IBD. IV iron demonstrated a higher efficacy in achieving a hemoglobin response of at least 2.0 g/dL (primary

TABLE 3. Summary of Findings

	Illustrative Comparative Risks (95% CI)		
	Assumed Risk Oral Iron	Corresponding Risk IV Iron	
Hemoglobin increase ≥ 2 g/dL	520 per 1000	633 per 1000 (555–704)	Relative effect (95% CI): OR, 1.59 (1.15, 2.20) No. of participants: 694 No. of RCTs: 5 Quality of evidence (GRADE): ⊕⊕⊕⊕ (moderate) Relative effect (95% CI): OR, 0.24 (0.12, 0.49)
Treatment discontinuation due to adverse events or intolerance	109 per 1000	29 per 1000 (14–57)	No. of participants: 694 No. of RCTs: 5 Quality of evidence (GRADE): ⊕⊕⊕⊕ (moderate) Relative effect (95% CI): OR, 5.45 (1.35, 22.0) No. of participants: 675 No. of RCTs: 4 Quality of evidence (GRADE): ⊕⊕⊕⊕ (very low)
SAEs	4 per 1000	21 per 1000 (5–81)	

Population: IBD patients with iron-deficiency anemia.

Intervention: intravenous (IV) iron supplementation for correcting anemia.

Comparison: oral iron supplementation.

Follow-up: 2–20 wk.

The basis for calculating the assumed (control group) risk is the overall event rate across the trial groups receiving oral iron.

The corresponding (IV group) risk is based on the assumed (control group) risk and the relative effect estimate (odds ratio).

The relative effect estimate and its 95% CI come from a fixed-effects meta-analytic model.

The overall quality of the synthesized evidence is judged as “moderate” for the following reasons: Data were derived from RCTs (randomized study design is considered the gold standard for assessing therapeutic interventions); the meta-analytic effect estimates are relatively precise (except for SAEs); the results are consistent (heterogeneity was very low across studies); but all the RCTs included in the meta-analysis are characterized by high RoB, because participants and personnel were not blinded to the intervention (a fact that downgrades the quality of evidence). A moderate quality of evidence means that “we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.”³¹

CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, IBD = inflammatory bowel disease, OR = odds ratio, RCT = randomized controlled trial, RoB = risk of bias, SAE = serious adverse event.

outcome) as compared to oral iron supplementation. Treatment discontinuation rates due to adverse events or intolerance were also lower among patients receiving IV iron preparations. Similarly, the occurrence of gastrointestinal adverse events (nausea, vomiting, abdominal pain, and diarrhea) was consistently lower in the IV iron study groups in comparison to the oral iron groups. Alarming, SAEs were more frequently reported among patients receiving IV iron preparations. However, the majority of the reported events were judged by the Safety Boards as unrelated or unlikely to be related to the study medication; thus a causal relationship cannot be inferred.

In the recent literature we have identified 3 relevant systematic reviews^{14,42,43} discussing the diagnosis and treatment of anemia in IBD. The review by Nielsen et al⁴² was wide in scope and included several randomized and nonrandomized prospective studies, with or without control groups, but did not include a meta-analysis. The earlier review and meta-analysis by Avni et al⁴³ did not include the recent larger trial by Reinisch et al,³⁸ which contributed about half the patients in our analysis. In addition, Avni et al⁴³ performed an “as-treated” (per-protocol) analysis, while ours was by intention-to-treat; the latter is recommended as the least biased way to estimate intervention effects in randomized trials.⁴⁴ They found a pooled effect estimate similar to our own (Relative Risk: 1.25, 95% CI: 1.04, 1.51) but our analysis improves the precision and reliability of this finding. Finally, we have the very recent systematic review and meta-analysis by Abhyankar and Moss,¹⁴ which had failed to find any significant difference between IV and oral iron on hemoglobin response, and was the motivation for undertaking our new review. That study included the same 5 trials (ie, we could not identify any additional trials) but was compromised by important data extraction errors (see Appendix, <http://links.lww.com/MD/A611>); ultimately its conclusions came out as invalid, since our rerun of the meta-analysis clearly demonstrates a statistically significantly higher efficacy of IV iron in achieving a hemoglobin response of at least 2.0 g/dL compared to oral iron.

In our study, a rigorous and extensive literature search was conducted; data extraction was carefully undertaken by 2 independent reviewers; studies were analyzed on an intention-to-treat basis; and appropriate meta-analytic methods were applied in the evidence synthesis to account for sparse data and imbalanced study groups. Moreover, though the primary studies had different inclusion and exclusion criteria, and follow-up duration, very little heterogeneity was identified across all analyses, supporting the robustness of our findings. However, our meta-analysis has some limitations. All the included trials were characterized by high RoB, as assessed with the Cochrane Collaboration’s tool; treatments were not evaluated in terms of cost, which is a key consideration in clinical practice; and no distinction was made between different preparations of IV or oral iron. According to GRADE, the quality of evidence (certainty of associations) in this review is moderate. This evidence, along with the treatment costs, patients’ values and preferences,⁴⁵ and other factors (clinical disease activity, severity of anemia, and previous intolerance to oral iron) should be considered to inform clinical decision making. Nevertheless, further high-quality (and adequately powered) randomized research, with clearly defined patient populations (eg, UC or CD, with mild, moderate, or severe anemia, etc.), would be very welcome, and may be necessary to extend our current knowledge on the alternative treatment modalities for correcting iron-deficiency anemia in patients with IBD.

In conclusion, synthesis of the existing randomized evidence supports that IV iron is more effective and better tolerated than oral iron supplementation for correcting anemia in adult patients with IBD.

REFERENCES

1. Fiorino G, Allocca M, Danese S. Commentary: anaemia in inflammatory bowel disease—the most common and ignored extra intestinal manifestation. *Aliment Pharmacol Ther*. 2014;39:227–228.
2. Fiorino G, Allocca M, Danese S. Anemia in inflammatory bowel disease: the opening of Pandora’s box? *Clin Gastroenterol Hepatol*. 2015;13:1767–1769.
3. Bager P, Befrits R, Wikman O, et al. High burden of iron deficiency and different types of anemia in inflammatory bowel disease outpatients in Scandinavia: a longitudinal 2-year follow-up study. *Scand J Gastroenterol*. 2013;48:1286–1293.
4. Abitbol V, Borderie D, Polin V, et al. Diagnosis of iron deficiency in inflammatory bowel disease by transferrin receptor-ferritin index. *Medicine (Baltimore)*. 2015;94:e1011.
5. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol*. 2008;103:1299–1307.
6. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol*. 2010;7:599–610.
7. Gasche C, Lomer MC, Cavill I, et al. Iron, anaemia, and inflammatory bowel diseases. *Gut*. 2004;53:1190–1197.
8. Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9:211–222.
9. Gomollón F, Gisbert JP. Anemia and inflammatory bowel diseases. *World J Gastroenterol*. 2009;15:4659–4665.
10. Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2006;12:123–130.
11. Ershler WB, Chen K, Reyes EB, et al. Economic burden of patients with anemia in selected diseases. *Value Health*. 2005;8:629–638.
12. Lee TW, Kolber MR, Fedorak RN, et al. Iron replacement therapy in inflammatory bowel disease patients with iron deficiency anemia: a systematic review and meta-analysis. *J Crohns Colitis*. 2012;6:267–275.
13. Stein J, Bager P, Befrits R, et al. Anaemia management in patients with inflammatory bowel disease: routine practice across nine European countries. *Eur J Gastroenterol Hepatol*. 2013;25:1456–1463.
14. Abhyankar A, Moss AC. Iron replacement in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2015;21:1976–1981.
15. Danese S, Fiorino G, Allocca M, et al. Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials. PROSPERO 2015:CRD42015024697. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024697. [Accessed 27 December 2015].
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269W64.
17. WHO, UNICEF, UNU. *Iron Deficiency Anemia: Assessment, Prevention and Control*. Report of a joint WHO/UNICEF/UNU consultation. Geneva: World Health Organization; 1998.
18. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356:1255–1259.

19. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
20. Bonovas S, Lytras T, Nikolopoulos G. On the criteria used for assessing the risk of bias in randomized trials included in systematic reviews and meta-analyses addressing adverse effects. *Eur J Epidemiol*. 2015;30:249–250.
21. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351–1375.
22. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
24. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Techn Bull*. 1999;8:15–17.
25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101.
26. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
27. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;810:101–129.
28. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
30. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011, version 5.0.1. Available from: www.cochrane-handbook.org.
31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
32. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
33. R Development Core Team. *R, A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014. <http://www.R-project.org/>. [Accessed 27 December 2015].
34. Schwarzer G. meta: an R package for meta-analysis. *R News*. 2007;7:40–45.
35. Erichsen K, Ulvik RJ, Nysaeter G, et al. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. *Scand J Gastroenterol*. 2005;40:1058–1065.
36. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol*. 2008;103:1182–1192.
37. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol*. 2009;44:838–845.
38. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monoferr) compared with oral iron for treatment of anemia in IBD (PROCEED). *Am J Gastroenterol*. 2013;108:1877–1888.
39. Schröder O, Mickisch O, Seidler U, et al. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease—a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol*. 2005;100:2503–2509.
40. Chassin MR, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. *JAMA*. 1998;280:1000–1005.
41. Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. *Lancet*. 2015; pii: S0140-6736(15)60865-0 [doi:10.1016/S0140-6736(15)60865-0].
42. Nielsen OH, Ainsworth M, Coskun M, et al. Management of iron-deficiency anemia in inflammatory bowel disease: a systematic review. *Medicine (Baltimore)*. 2015;94:e963.
43. Avni T, Bieber A, Steinmetz T, et al. Treatment of anemia in inflammatory bowel disease—systematic review and meta-analysis. *PLoS ONE*. 2013;8:e75540.
44. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol*. 1992;21:837–841.
45. Danese S, Hoffman C, Vel S, et al. Anaemia from a patient perspective in inflammatory bowel disease: results from the European Federation of Crohn's and Ulcerative Colitis Association's online survey. *Eur J Gastroenterol Hepatol*. 2014;26:1385–1391.