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Research Article

Treatment of Iron Deficiency Anemia in Inflammatory Bowel Syndrome Patients

Al Nihab Ali Naji A[1]*, Feras Mohammed Omair Al Habshan[2], Albesher, Sarah Mohmmed[3], Mohammed Salem Alqithami[4], Rawan Adel Mohammed[5], Essraa Talal Kouma[3], Alarjan Abdulrahman Wufuq[6], Mada Salim Almatrafi[2], Hezab Abdulrahman T Alrayes[6], Saud Ali Ahmed Alzahrani[7], Anas Mohammed Aljoaid[4], Ahmed Saeed Ali Saleh[8], Mohammed Abdullah Al-Arim[8], Aymen Abdulrzag Khadrawi[4], Abdulmohsin Nami Almutairi[9], Israa Mohammed Alammari[5]

[1]Anak General Hospital, Eastern Province, KSA

[2]Ibn Sina College, Jeddah, Saudi Arabia

[3]King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

[4]Umm Al-Qura University, Mecca, Saudi Arabia

[5]Al-Maarefah Collage, Diriyah, Saudi Arabia

[6]Aljouf University, Sakakah, Saudi Arabia

[7]Albaha University, Al Bahah, Saudi Arabia

[8]King Khalid University, Abha, Saudi Arabia

[9]King Abdul Aziz, Jeddah, Saudi Arabia

***Corresponding Author**: Al Nihab Ali Naji A, Anak General Hospital, Eastern Province, KSA.

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Abstract

Background: Anemia is multifactorial in nature with iron deficiency anemia (IDA) being the most predominant etiological forms of chronic disease. Anemia is a common extraintestinal manifestation of inflammatory bowel disease (IBD) and is frequently overlooked as a complication. While oral iron supplementation has traditionally been a mainstay of IDA treatment, it has also been linked to extensive gastrointestinal side effects and possible disease aggravation.

Aim of the Study: provide all available evidence regarding the safety and efficacy of therapy existing today to correct anemia in IBD.

Methods: A review of the scientific literature (Pubmed, Embase, Cochrane Library and CENTRAL) from 1970 to 2017 identify randomized controlled trials that investigated the management and treatment of iron deficiency anemia in inflammatory bowel syndrome patients were the primary endpoints. Study quality was assessed using PRISMA and a best evidence synthesis was performed.

Results: The search yielded seven studies fulfilled the inclusion criteria, with a total of 899 patients, of which 337 patients (37.5%) suffered from Crohn's disease (CD) and 562 (62.5%) from ulcerative colitis, with a mean age of 37.4, 61.6% females. IV iron was superior to oral iron administration with a higher Hb response rate with higher safety profile and less adverse effects; RR 1.25 (95% CI 1.04 - 1.51, I2 = 2%, 4 trials), while CRP levels and disease activity indexes were not significantly affected by IV iron.

Conclusion: Due to the in adequate iron absorption of the orally administrated iron supplement and negative effect on disease activity in IBD patient, IV iron administration is by far recommended for the treatment of the iron deficiency anemia which provides a more efficient and safer line treatment for the patients of concern.

Keywords: *Anemia; Inflammatory Bowel Disease; Crohn's Disease; Iron Desorption; Ulcerative Colitis*

Introduction

Iron as an Essential Element for Blood Production

Iron is an essential mineral for the function of all body cells and is absorbed at the apical surface of enterocytes to be transported by ferroportin, the only known iron exporter, across the basolateral surface of the enterocyte into circulation [1].

The body requires iron for the synthesis of its oxygen transport proteins, in particular hemoglobin and myoglobin, and for the formation of heme enzymes and other iron-containing enzymes involved in electron transfer and oxidation-reductions [2]. Almost two-thirds of the body iron is found in the hemoglobin present in circulating erythrocytes, 25% is contained in a readily mobilizable iron store, and the remaining 15% is bound to myoglobin in muscle tissue and in a variety of enzymes involved in the oxidative metabolism and many other cell functions [3].

The average adult harbors at least 3 - 4 g of stored iron that is balanced between physiologic iron loss and dietary intake. Most iron is incorporated into hemoglobin (Hb), whereas the remainder is stored as ferritin, myoglobin, or within iron-containing enzymes. About 20 - 25 mg of iron is needed daily for heme synthesis. Approximately 1 - 2 mg of this requirement comes from dietary intake, and the remainder is acquired by recycling iron from senescent erythrocytes [4]. Total iron loss averages about 1 - 2 mg/day, mostly via the feces and cellular desquamation from the skin and intestine, as well as additional losses through menstruation [5].

Iron Deficiency Anemia

Iron deficiency anemia is the most common form of anemia worldwide, representing up to 50% of all cases [6]. Causes of iron deficiency include poor iron intake, chronic blood loss, impaired absorption, or any combination of the three [7]. Blood loss from the gastrointestinal (GI) tract is the most common cause in men and postmenopausal women and is a common reason for referral to a gastroenterologist [8].

Iron Deficiency in IBD

Anemia represents the most common systemic complication and/or extraintestinal manifestation in inflammatory bowel disease (IBD) [9], both at diagnosis and during flare-ups, [10] exceeding without a doubt the frequency of extraintestinal manifestations (e.g. rheumatic, dermatologic, and ophthalmologic) [11]. A systematic review conducted by Filmann., *et al.* [12] which was published between 2007 and 2012 reported a prevalence of anemia in patients with Crohn's disease of 27% (95% confidence interval, 19 - 35) and of 21% (95% confidence interval, 15 - 27) in patients with ulcerative colitis. More than half of the anemic patients (57%) were found to be iron deficient [12]. This huge variation may be due to differences in the study populations (e.g. hospitalized patients vs. outpatients) as well as in the definition of anemia.

In a more recent study [13], a prevalence of anemia in IBD patients was reported to be 20% among outpatients 7 and 68% among hospitalized patients.

Iron deficiency in IBD is caused by numerous factors, including increased iron loss from bleeding due to gastrointestinal inflammation and decreased iron absorption as a consequence of short bowel syndrome, loss of appetite during IBD flares, and inflammation-driven blockage of intestinal iron acquisition and macrophage iron reutilization [14].

Patients with active IBD suffer from chronic blood loss due to mucosal bleeding, which often causes true iron deficiency, as reflected by low ferritin levels [15]. Furthermore, true iron deficiency and anemia reduce hepcidin expression. These effects are transmitted by iron-deficiency-mediated inhibition of SMAD signaling in hepatocytes, anemia-induced and erythropoiesis-driven formation of hepcidin inhibitors such as erythroferron and growth differentiation factor 15 (GDF-15), and hypoxia-driven blockade of hepcidin formation via platelet-derived growth factor BB (PDGF-BB) or hypoxia-inducible factors (HIFs) [16]. Thus, in the presence of both inflammation and true iron deficiency due to bleeding in IBD, circulating hepcidin levels decrease because anemia and iron-deficiency regulatory signals dominate inflammation-driven hepcidin induction [17]. Therefore, truly iron-deficient patients, even in the presence of systemic inflam-

mation, are able to absorb considerable amounts of iron from the intestine [18]. If patients have more than 20 bowel movements per day and report that food appears in the rectum 30 minutes after uptake, it is easy to imagine that a sufficient absorption time in the small bowel is not present [19]. This is also indicated by the fact that patients with severe ulcerative colitis may have reduced serum protein and albumin levels indicating a malabsorption. An additional mechanism that antagonizes iron absorption in the gut is discussed below. The second major reason for an iron deficiency in IBD certainly is the continuous blood loss in active colitis or ileitis associated with a depletion of iron and iron stores [20].

In the present review, we aim to assess the optimal treatment intervention to manage iron deficiency anemia in Patients with IBD.

Materials and Methods

Data Sources

We carried out a systematic review for randomized control trials study of patients with iron deficiency anemia couples with Inflammatory bowel disease.

Databases searched included Book Citation Index - Science (since 2005), Cumulative Index to Nursing and Allied Health, Conference Proceedings Citation Index - Science (since 1990), Embase, Google Scholar, PubMed/MEDLINE, Scopus, The Cochrane Library, and Web of Science. Keywords, phrases, and MeSH terms searched included "IBD," "iron deficiency anemia," "Inflammatory bowel disease," "IV iron supplement," and "treatment". A PubMed/MEDLINE search example is (("IBD" [MeSH]) OR "IBD" OR "Crohn's disease" OR ulcerative colitis," were searched as both medical subjects heading terms (MeSH) and as text words and crossed with "iron" (MeSH and a text word) and specific iron preparations; "erythropoietin stimulating agents" and specific ESA preparations and "anemia"). Authors independently reviewed titles and abstracts and then downloaded relevant studies. References were reviewed for additional studies.

Study Selection and Criteria

Search results were screened by scanning abstracts for the following:

Inclusion Criteria:

1. Study design: randomized controlled trials (RCTs) only.
2. Comparative studies (RCTs) comparing different treatment approached for anemia in patients with IBD.
3. ALL RCTs meeting the same endpoints of the present review regardless of publication status (published, conference proceedings, or unpublished), trial years, and language.

Exclusion Criteria:

1. Articles with study design other than RCTs.
2. Studies not meeting the primary outcome of the present review.

Outcomes

• **Primary Outcome:** Effect of treatment for anemia in IBD on the hemoglobin response

• **Secondary Outcomes:** Disease severity scores:

a. (Inflammatory Bowel Disease Questionnaire (IBDQ) scores [20]

b. The Harvey-Bradshaw Simple Index scores (HBSI) [21],

c. Crohn's Disease Activity Index (CDAI) diary card [22] and UC [23]);

e. iron indices (ferritin concentration and transferrin saturation (TSAT),

f. Hb levels or absolute change in Hb level at the end of follow-up; red blood cell transfusion requirements,

g. inflammatory markers (CRP levels); number of patients with treatment failure; adverse effects (AEs) (severe AEs, AEs leading to discontinuation and by involved organ), QOL scores, and mortality.

Data Extraction

We assessed trials for methodological quality and examined the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective outcome reporting.

Results

The initial search was broad, accepting any article related to iron deficiency anemia in IBD patients to ensure a comprehensive view of available work, and generated 158 articles. Preliminary application of study criteria identified 103 potential studies for inclusion that met one or more criteria after removing duplication. Further screening of abstracts yielded 44 articles then followed by a third round of filtration while carefully applying the inclusion and exclusion criteria. Accordingly, another review of these investigations excluded 37 publications and finally yielded 50 RCTs that fully met all inclusion criteria. No individual authors were contacted for information. No further review of methodological quality of the studies was conducted beyond that it appeared in a peer review journal and comprised an RCT. The 7 eligible articles were again closely examined and data extracted using a standard protocol regarding target population, sample size, program provider, program content, intervention components, processes, and outcomes. Comparison among provider type was computation of differences between percent of successful program to number attempted. No further statistical analyses were employed.

Finally, 7 studies were included and detailed as the focus for the present study. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22-28] in reporting the results (Figure 1).

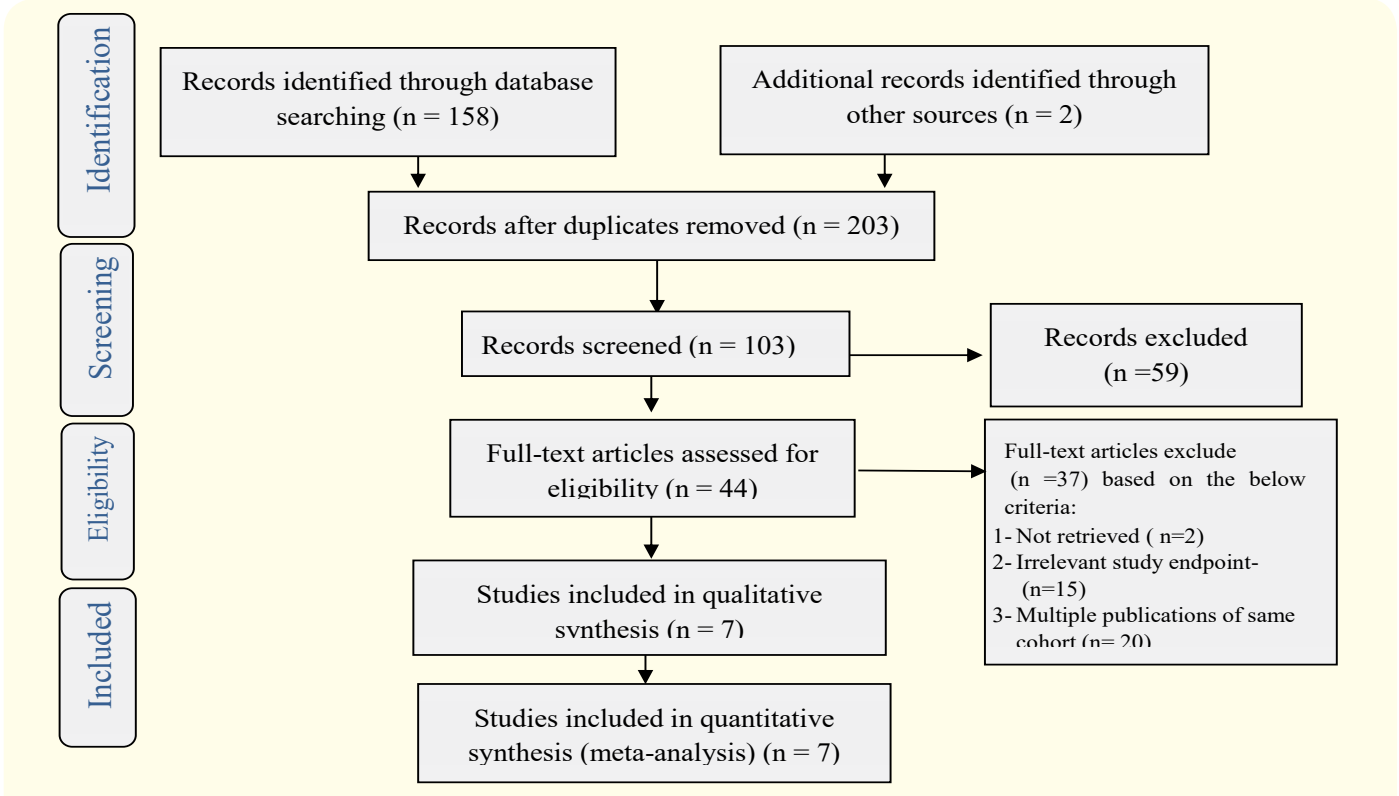

Figure 1: *PRISMA flow diagram showing the selection criteria of assessed the studies [21].*

The search yielded seven studies fulfilled the inclusion criteria.

A total of 899 patients were recruited in the selected studies, of which 337 patients (37.5%) suffered from Crohn's disease (CD) and 562 (62.5%) from ulcerative colitis (UC) with a mean age of 37.4, female % was 61.6% and a mean HB level of 10.6 at enrollment. All trials included patients with anemia, despite the fact that the definition of anemia varied substantially between the trials (Table 1).

Four trials [24-27] compared oral to IV iron 24 while 1 trial compared two oral iron preparations [28]. Evstatiev., *et al*. [23] compared two IV iron preparations while Kulnigg-Dabsch., *et al*. [22] compared IV iron to placebo.

IV vs. OP iron

Planned total IV iron dosages was in the range of 1,000 mg to 2,000 mg while the reported administered dosages ranged from 980 mg to 1,700 mg.

Follow up period was between 6 - 20 weeks, without reported losses to follow up. All patients suffered from anemia at enrolment, however, due to different inclusion criteria, in the trial by Erichsen., *et al.* [27] patients had a higher baseline Hb level and a higher TSAT. Ferritin levels were significantly low at enrolment (median values ranged from 5.0 to 19 μg/L).

Noteworthy, patients had also more dormant disease at admission in appraisal to studies conducted by Schroder et al. 26 and Kulnigg., *et al.* [25] as presented by higher CAI, CDAI and HBSI scores (Table 1).

Authors	Year of Pub.	No. of Patients	Mean Age	No. of Females	% Females	Mean Hb (g/dL) at enrolment	% patients with CD/UC	Disease severity score (CAI, HBSI, CDAI)
Kulnigg-Dabsch., *et al*. [22]	2013	16	36.1	12	75	11.7	68/32	m 5 (2), NS, med 168 (99-229)
		9	31.6	7.92	88	11.1	44/56	m 4 (1), NS, med 187 (116-207)
Evstatiev., *et al*. [23]	2011	244	39.5	146.4	60	10.1	35/65	m 3.7 (2.1), NS, m 97.5 (61.2)
		239	38	138.62	58	10.3	31/69	m 3.2 (2.2), NS, m 84.5 (61.7)
Lindgren., *et al*. [24]	2009	45	42	31.95	71	10.5	44/56	med 3.4 (0-10), med 3.9 (0-12), NS
		46	42	30.82	67	10.4	52/48	med 3.1 (0-8), med 3.2 (0-8), NS
Kulnigg., *et al*. [25]	2008	136	40	80.24	59	8.7	30/70	med 8 (0-14), NS, med 217 (72-424)
		60	45	36	60	9.1	26/74	med 7 (0-15), NS, med 238 (63-363)
Schroder., *et al*. [26]	2005	22	35	16.94	77	9.8	77 23	med 11 (7-19), NS, med 217 (46-417)
		24	33	16.8	70	9.6	50/50	med 8 (4-11), NS, med 281 (71-423)
Erichsen., *et al*. [27]	2005 (1)	17	18 - 46 (range)	11.56	68	10.6-11.6	57/43	med 1 (0-3)/1 (0-4), med 3.5 (1-7)/4 (2-5), NS
Erichsen., *et al*. [28]	2005 (2)	21	41	12.81	61	13.1	62/38	med 1 (0-7), med 3 (0-8), NS
		20	31	12	60	12.5	55/45	med 2 (0-5), med 2 (0-10), NS
Total	8 studies	899	37.4	554.1	61.6	10.6	631/669	

Table 1: The characteristics of the included studies with the severity of disease of the enrolled patients.

Treatment protocol and dosages are captured in details in (Table 2) for all RCTs.

Treatment Protocol					
Authors	**Year of Pub.**	**Drug and dosage**	**Maximal planned dosage of iron**	**Follow up duration**	**Haematological Inclusion Criteria: TSAT (%)/Ferritin (ng/mL)/Hb (g/dL)**
Kulnigg-Dabsch., *et al*. [22]	2013	IV Ferric carboxymaltose 500 mg, once every 2 weeks, 3 weeks	1,500 mg IV	6 weeks	<20%,<100,>10.5
		placebo	NA		
Evstatiev., *et al*. [23]	2011	IV Ferric carboxymaltose 500-1,000 mg, once weekly, 3 weeks	3,000 mg	12 weeks	NS,>100,7-12/13
		IV iron sucrose 200 mg, 1-2 times weekly, 3 weeks	2,200 mg		
Lindgren., *et al*. [24]	2009	IV iron sucrose 200 mg, once every 1-2 weeks, 20 weeks	8,000 mg IV	20 weeks	NS,<300,<11.5
		Oral ferrous sulphate, 400 mg daily, 20 weeks	56,000 mg PO		
Kulnigg., *et al*. [25]	2008	IV Ferric carboxymaltose 500-1,000 mg, once every 4 weeks, 12 weeks	3,000 mg IV	12 weeks	<20%,<100,<11
		Oral ferrous sulphate, 200 mg daily, 12 weeks	16,800 mg PO		
Schroder., *et al*. [26]	2005	IV iron sucrose 200 mg, 1-2 per week, 5 weeks	2,500 mg IV	6 weeks	<20%, <20, <10.5/11
		Oral ferrous sulphate, 100-200 mg daily, 5 weeks			
Erichsen., *et al*. [27]	2005 (1)	IV iron sucrose 200 mg, 3 times over 2 weeks	600 mg	2 weeks	NS,NS, <12/13
		Oral Ferrous fumarate, 120 mg daily, 2 weeks	1,680 mg		
Erichsen., *et al*. [28]	2005 (2)	Oral ferrous sulphate, 200 mg daily, 2 weeks	2,800 mg	2 weeks	NS,<15, NS
		Oral Maltofer Film tablets, 200 mg daily, 2 weeks	2,800 mg		

Table 2*: Treatment regimen/protocol for the enrolled cases in the included studies.*

Primary Outcome

A Meta- analysis conducted by Avni T., *et al*. [29] for 4 selected RCTs [22,24,26,27] provided a strong evidence that IV iron was associated with a higher rate of achieving a 2 g/dl increase in Hb concentration in comparison to oral iron; RR 1.25 (95% CI 1.04 - 1.51, I2 = 2%(for 4 selected trials (Table 3).

	Intravenous Iron		Oral Iron		Risk Ratio	
	Events	Total	Events	Total	weight	M-H, Fixed, 95% CI
Kulnigg-Dabsch., *et al*. [22]	3	17	0	17	0.70%	7(0.39,125.99)
Lindgren., *et al*. [24]	85	111	33	49	60%	1.14(0.91,1.42)
Schroder., *et al*. [26]	30	45	21	46	27.20%	1.46(1.00,2.13)
Erichsen., *et al*. [27]	10	18	9	17	12.10%	1.05(0.57,1.93)
Total(95%CI)		191.0		129.0	1.0	1.25(1.04,1.51)

Table 3: *IV iron versus PO iron, Hb response at end of follow-up.*

Iron indices

Ferritin levels were remarkably elevated with IV iron treatment in comparison to oral iron preparation by a WMD of 107.5 ng/mL (95% CI 24.7 - 190.2, I^2 = 99%, random effects model), however, the trials were significantly heterogeneous with no single study accounting for it. TSAT was not significantly affected with either intervention achieving an absolute decrease of WMD 0.91% (95% CI - 7.87 - 6.05, I^2=97%, random effects model) with IV iron. The IV route was associated with a greater improvement in the Hb level than the oral route, WMD in Hb of 0.2 g/L (95% CI 0.02 - 0.39, I^2 =95%, random effects model).

IV FCM versus placebo

One study [22] compared FCM to placebo. There were no data regarding Hb response. Iron indices (ferritin, TSAT) and Hb level improved significantly with FCM but not with placebo. QOL and disease severity scores improvement and the occurrence of serious AEs were similarly improved with both interventions without statistically significant advantage in either treatment.

IV Ferric Carboxymaltose (FCM) versus IV iron sucrose

A trial by Evstatiev., *et al*. [23] put in comparison FCM with iron sucrose. Follow up time was 12 weeks. FCM was associated with a higher rate of achieving a 2 g/dl increase in Hb concentration in comparison to iron sucrose by a RR of 1.65 (95% CI 1.11 - 2.38). Improvement in QOL scores and disease severity scores were not different between the study arms. The occurrence of serious AEs was not different between interventions.

Discussion

In the present review, we aimed to assess the current evidence for the treatment of anemia in IBD patients. We conducted several comparisons, the important one being the comparison of IV iron to oral iron. The important findings of our meta-analysis include the better Hb response achieved with IV iron preparations compared to oral iron, with an acceptable safety profile and higher rates of adherence or reduced discontinuation of intervention in the IV iron arm.

Moreover, a significant increase in ferritin level and Hb value (as a continuous variable) with IV iron therapy was clearly observed. Likewise, disease activity indexes were not negatively influenced by IV iron. CRP values and QOL scores were unaffected by either preparations (although reporting methods and measurement scales varied considerably between studies). Unfortunately, though, there were not enough data to consider further analyses of Hb response according to disease type, presence of any anemia or iron deficiency anemia at enrollment, type of iron preparation and methodological sensitivity analyses.

As for the optimal IV iron preparation, the comparison of IV versus oral iron included 3 trials of iron sucrose and one of FCM, all showing similar results. Only one trial compared between iron sucrose and FCM [23] and FCM proved to be more efficacious than iron sucrose in achieving hemoglobin response. FCM is more convenient to patients because which usually requires only one to two infusions (up to 1 g per dose), while iron sucrose usually requires five to 10 infusions to reach total dose because 200 mg is considered the well tolerated individual dose. In a previous meta-analysis, FCM was demonstrated to be superior to iron sucrose and oral iron in achieving an increased HB level with a similar rate of serious AEs and mortality [29].

The tendency towards an enhanced Hb response with the use of Erythropoietin stimulating agents (ESA) complemented with IV iron was also studied and no serious adverse events were observed. This is perhaps due to the fact that anemia in IBD is multi-factorial with anemia of chronic disease is just one of the mechanisms.

In addition to that, ESA has proved to be efficient in achieving hemoglobin response in other forms of anemia of chronic disease as chronic kidney disease and cancer related anemia [30].

The advantages of IV iron over oral therapy have been demonstrated previously in other clinical settings. IV iron was proven to be superior to oral iron replacement in achieving Hb response, in patients suffering from chronic kidney disease and especially when on dialysis. IV iron added to ESA resulted in an increase in Hb response and a reduction in the need for red blood cell transfusions in patients with chemotherapy-induced anemia [32]. IV iron therapy was also associated with improved quality of life parameters, reduction in hospitalizations, and increased exercise performance in patients with symptomatic chronic heart failure [33]. No increased risk of serious adverse events was found in these meta-analyses. ESAs have also been shown to be effective in improving Hb levels and quality of life in several chronic conditions (dialysis, chronic heart failure, cancer [34], rheumatoid arthritis [35]), although an increased risk for thromboembolism and mortality was found in some studies [36].

Evidence for treatment with iron supplements for iron deficient and anemic patients, and with ESA for ACD was graded as grade A and grade B recommendations, respectively. The preferred route of iron supplementation in IBD according to an international working party guidelines [37] is IV (Grade A). For ESA, treatment should be combined with IV iron supplementation (grade A) [38]. Our results are in agreement with these 2007 guidelines.

Finally, it should be highlighted that iron deficiency in IBD often relapses after iron replenishment [39]. Consequently, periodically monitoring, for example, every 3 months for a year and again after a year once the Hb value is normalized and iron stores are replenished to assess if retreatment is required. However, we lack solid data on when to stop iron supplementation therapy in order to avoid iron overloading, which may cause side effects because of the potential of the metal to catalyze the formation of toxic radicals [40].

However, prospective studies will be necessary to clarify the impact of anemia correction and iron supplementation on the course of IBD and patient outcomes, as well as the definition of clinical endpoint, in order to optimize anemia management and iron supplementation in IBD patients.

Limitation of the Review

- The included trials had different follow-up duration ranging from 2 to 20 weeks, however most trials that examined IV iron followed their patients for a similar amount of time (12 - 20 weeks).
- Hb values for the definition of anemia (or inclusion criteria) and for the primary outcome of Hb response varied between studies.
- The protocols used for interventions (although similar) did differ between trials.
- The actual amount of elemental iron delivered for the patients due to the different administration schedules and the bioavailability of the different compounds may also play a role in determining the actual Hb response.

Conclusion

Our findings strengthen the recommendation of IV iron as the preferred route according to the better hemoglobin response achieved. Although we did not prove a change in QOL and disease severity score with the use of IV iron, and we lacked data regarding QOL in other interventions, there is some evidence that all iron interventions decrease the disease severity score.

Implications for practice and research: Treatment for anemia in IBD should include iron. The preferable route according to current evidence is IV and not oral iron replacement, due to improved hemoglobin response, no added toxicity and no negative effect on disease activity. ESA therapy may also be used in order to treat the anemia of chronic disease that usually accompanies iron deficiency in IBD. As for the optimal IV iron type and schedule - future trials should further explore the most efficacious administration schedule and dosages by directly comparing between the different iron compounds and schedules. In order to define the role of ESA, future trials should compare IV iron to IV iron with the addition of ESA.

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