Scandinavian Journal of Gastroenterology, 2009; 44: 838–845

informa
healthcare

ORIGINAL ARTICLE

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

STEFAN LINDGREN[1], OLA WIKMAN[2], RAGNAR BEFRITS[3], HÅKAN BLOM[4], ANDERS ERIKSSON[5], CHRISTER GRÄNNÖ[6], KJELL-ARNE UNG[7], HENRIK HJORTSWANG[8], ANDERS LINDGREN[9] & PETER UNGE[10]

[1]*Department of Medicine, Gastroenterology-Hepatology Division, University Hospital MAS, Malmö,* [2]*Department of Medicine, Södersjukhuset, Stockholm,* [3]*Department of Gastroenterology and Hepatology, Karolinska Hospital, Stockholm,* [4]*Department of Medicine, Sunderby Hospital, Lulea and Östersund Hospital, Östersund,* [5]*Department of Internal Medicine, Gastroenterology Unit, Sahlgrenska University Hospital/Östra Sjukhuset, Göteborg,* [6]*Department of Medicine, Ryhov Hospital, Jönköping,* [7]*Department of Medicine Kärnsjukhuset, Skövde,* [8]*Department of Endocrinology and Gastroenterology, University Hospital, Linköping,* [9]*Department of Medicine, Borås Hospital, Borås, and* [10]*Department of Medicine, Bollnäs Hospital, Bollnäs, Sweden*

Abstract

Objective. Patients with inflammatory bowel disease (IBD) often have low iron stores or anaemia. There is controversy about whether iron should be supplemented orally or intravenously (i.v.). The purpose of this study was to investigate whether treatment with intravenous iron is superior to treatment with oral iron. The primary end-points were response and remaining anaemia at the end of treatment (EOT). ***Material and methods.*** Ninety-one patients with IBD and anaemia (B-Hb <115 g/L) were randomized to oral iron sulphate ($n=46$) or intravenous iron sucrose ($n=45$) treatment for 20 weeks. ***Results.*** Forty-three patients in the intravenous iron group completed the study compared to 35 patients in the oral iron group ($p=0.0009$). Only 22 patients (48%) tolerated the prescribed oral dose, and 52% reduced the dose or withdrew from treatment because of poor tolerance. At EOT, 47% patients in the oral iron group increased their B-Hb by ≥ 20 g/L, compared with 66% in the intravenous iron group ($p=0.07$). In the oral iron group, 41% still had anaemia versus 16% of the patients in the intravenous iron group ($p=0.007$), and 22% versus 42% reached their reference B-Hb level ($p=0.04$). Treatment with intravenous iron sucrose improved iron stores faster and more effectively than oral iron ($p=0.002$). Under treatment with intravenous iron, 74% of the patients had no anaemia and normal S-ferritin levels (>25 μg/L) at EOT compared with 48% of patients receiving oral iron ($p=0.013$). ***Conclusions.*** Treatment with intravenous iron sucrose is effective, safe, well tolerated and superior to oral iron in correcting haemoglobin and iron stores in patients with IBD.

Key Words: *Anaemia, Crohn's disease, inflammation, iron, iron deficiency, iron sulphate, iron sucrose, ulcerative colitis*

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are frequently associated with anaemia. The reported rates vary widely, but at least one-third of patients with inflammatory bowel disease (IBD) have anaemia [1–3]. Only recently, the correction of anaemia in IBD has been highlighted as a specific therapeutic goal [2,4].

Iron is a component not only of haemoglobin and myoglobin but also of cytochromes and many other enzymes. Patients with IBD gradually adapt to a large variety of unspecific symptoms such as fatigue, malaise, weakness, breathlessness, nausea, irritability, poor concentration or even depression, which may be related to iron deficiency and anaemia. Quality of life of anaemic patients with Crohn's disease is actually comparable to that of patients with advanced cancer [2]. Several studies have shown that correction of iron deficiency and chronic anaemia has significant benefits for patients in their

Correspondence: Stefan Lindgren, MD, PhD, Department of Medicine, Gastroenterology-Hepatology Division, University Hospital MAS, SE-205 02 Malmö, Sweden. E-mail: Stefan.Lindgren@med.lu.se

(Received 19 December 2008; accepted 8 February 2009)

ISSN 0036-5521 print/ISSN 1502-7708 online
DOI: 10.1080/00365520902839667

general well-being and quality of life and hardly any negative consequences for disease activity [4,5].

The most common causes of anaemia in IBD are true iron deficiency owing to iron losses from inflammed bowel or dietary deficiency, or functional iron deficiency secondary to chronic inflammation [6]. It is estimated that a daily loss of 10 mL blood has to be balanced by an average daily iron intake of 15 mg, of which only 1–2 mg is absorbed.

Patients suffering from iron deficiency should primarily be treated with supplementary oral iron. However, patients with IBD often do not tolerate this formulation, mainly because of gastrointestinal side effects. This leads to low compliance or the abandonment of this particular treatment. In contrast, a number of studies have shown positive responses to iron infusion in patients with IBD [6,7], also when oral iron is not tolerated or gives an inadequate response [8]. The development of iron sucrose has circumvented the drawbacks of the hypersensitivity to iron dextran and it is regarded as safe also in patients who have previously reacted adversely to iron dextran [9,10].

Recently, in a short comparative study, oral and intravenous (i.v.) iron preparations were almost equally effective in increasing Hb in those patients who were able to complete the study, which lasted for 6 weeks [11]. The intolerance to oral iron was substantial, since almost one-third of the patients on oral iron left the study owing to intolerance, despite the rather low dose of prescribed oral iron (100 mg/day) and despite using ferrous glycine sulphate (Ferrosonol®), a formulation that has been proposed to have fewer adverse reactions among ferrous sulphate products. In addition, only patients tolerant to oral iron were included. Many patients were still anaemic and also iron deficient after the oral treatment, in contrast to the group that received i.v. iron sucrose treatment [11].

To further evaluate and compare the efficacy and tolerance of oral and i.v. iron treatment, the present study was extended to 20 weeks. The doses used were those recommended by the Summary of Product Characteristics (SPC). The primary endpoint was haemoglobin response to treatment after 20 weeks. In addition, we compared the efficacy in correcting iron deficiency.

Material and methods

Patients

Ninety-one patients with IBD were investigated at 11 centres in Sweden. The patients were randomized to either i.v. injections of iron sucrose or oral ferrous sulphate. Eligible patients were males and females aged 18–85 years suffering from UC or CD. The patients had B-Hb levels <115 g/L, verified at least twice (within 3 months) and S-ferritin concentrations <300 μg/L and iron deficiency defined by S-iron, transferrin and transferrin saturation (TSAT). The patients also signed an informed consent form.

Patients were not in an active relapsing stage of IBD, pregnant, or had any clinically significant haematological disease other than iron-deficiency anaemia or any other clinically significant disease/dysfunction, which in the opinion of the investigator disqualified them from this study. Fertile women were allowed to use contraceptives. Patients were also not eligible for participation if they were known to have symptomatic intestinal strictures and had been treated with oral or parenteral iron during the previous month. Other exclusion criteria were S-creatinine levels >250 μmol/L, deficiencies in cobalamin and/or folic acid, or contraindications for administration of iron sucrose or ferrous sulphate. Participation was not allowed if there were plans for significant surgery during the study period.

Demography

Patient age, diagnosis and disease activity at inclusion are presented in Table I.

The HBAI (Harvey–Bradshaw Activity Index) and WI (Walmsley Index) scores (range 0–21) (see below) indicate that the study population showed modest disease activity at inclusion. Despite this, the patients suffered from severe anaemia and had an even more pronounced iron deficiency at baseline, as indicated in Table II. There were no significant differences between the two groups in these respects at baseline.

Concomitant medication

Some study patients were receiving concomitant medication, which can interact with iron absorption and iron metabolism. Six patients were being treated with calcium supplements and 9 were receiving proton-pump inhibitors, which interfere with iron absorption. Six patients were taking salicylic acid as a thrombosis prophylaxis, which could lead to an increased occult blood loss in the gastrointestinal tract. Fifty-two patients (57%) were taking immunosuppressive drugs because of their inflammatory condition. There was no significant difference in the use of concomitant medication between the two groups.

S-transferrin receptor values were high and TSAT values were low at baseline, indicating a pronounced iron deficiency (Table II). S-ferritin was low in most

Table I. Patient age, diagnosis and disease activity at baseline.

	All	Iron sucrose	Iron sulphate
n	91	45	46
Age (years ± SD)	42.4 ± 15.7	42.1 ± 15.0	42.8 ± 16.5
Diagnosis M/F (*n*)	28/63	13/32	15/31
Crohn's disease (*n*)	44	20	24
Ulcerative colitis (*n*)	47	25	22
Disease activity (mean score)			
Crohn's disease – HBAI (range)	3.0 (2–5)	3.9 (0–12)	3.2 (0–8)
Ulcerative colitis – WI (range)	2.5 (1–5)	3.4 (0–10)	3.1 (0–8)

Abbreviations: HBAI = Harvey–Bradshaw Activity Index; WI = Walmsley's Index.

patients, but increased in a few, probably as a result of inflammation.

Iron preparations

The total dose of i.v. iron sucrose (Venofer®) (Vifor France SA, Neuilly-sur-Seine, France) was individually determined according to a dosage scheme as described in the SPC, which is based on the Ganzoni formula to calculate the total iron deficit [12]. The drug was given either in a single doses of 200 mg (10 mL) once a week, or every second week within the study period of 20 weeks until the cumulative dose was reached. The dose of iron sucrose was thus not the maximal weekly dose. According to the recommendations of the SPC, 500 mg iron sucrose should be given to replenish the iron stores. Since it has been shown earlier [8] that this dose seems to be an underestimation, 1000 mg was given to replenish the iron stores.

Ferrous sulphate tablets (Duroferon®) (Astra-Zeneca AB, Södertälje, Sweden) 100 mg 2 × 2 daily were given during the 20-week study period, but the dose could be reduced if not tolerated. Thus, the oral iron dose was the maximal dose, which could be tolerated.

Primary objectives and assessments

The primary objective was to compare the efficacy of intravenous iron sucrose with oral iron sulphate in raising B-Hb concentrations in anaemic patients. The primary efficacy parameter was response to treatment at week 20 (end of treatment, EOT). This was assessed by a B-Hb increase of >20 g/L, remaining anaemia at EOT and the proportion of patients reaching the mean B-Hb reference concentration (Table III) [13]. The secondary end-point was the efficacy in correcting iron deficiency.

Secondary objectives and assessments

Clinical activity was recorded in accordance with the HBAI [14] for CD and the WI [15] for UC. Safety was monitored by reporting vital signs, clinical chemistry and adverse events (AEs).

Table II. Blood and iron parameters at baseline by treatment group.

	Iron sucrose (*n* = 45) Mean ± SD	Iron sulphate (*n* = 46) Mean ± SD	*p*-value
B-Hb (g/L)	104.9 ± 9.0	103.8 ± 11.4	NS
S-ferritin (μg/L)	14.0 ± 17.6	12.4 ± 14.5	NS
MCV (fL)	80.4 ± 7.4	78.6 ± 8.5	NS
TSAT%	7.1 ± 5.3	6.5 ± 4.8	NS
Transferrin (g/L)	3.0 ± 0.6	3.1 ± 0.5	NS
S-EPO (IU/L)	48 ± 53	60 ± 101	NS
S-transferrin receptor (U/L)	2.7 ± 1.1	3.1 ± 1.2	NS
S-albumin (g/L)	36 ± 4	37 ± 5	NS
CRP (mg/L)	23 ± 25	18 ± 21	NS

Abbbreviations: TSAT = transferrin saturation; NS = not signifi cant; MCV = mean corpuscular volume; EPO = erythropoietin; CRP = C-reactive protein.

Table III. The targets for treatment with oral and i.v. iron sucrose [13].

	Females, mean	Males, mean
Reaching limit for anaemia, g/L	≥120 g/L	≥130 g/L
Reaching mean reference Hb, g/L	130 g/L	150 g/L
No iron deficiency	S-ferritin >100 μg/L or TSAT >30%	

Abbreviation: TSAT = transferring saturation; i.v. = intravenous.

Sample size

Sample size calculation was based on the significance level of 5% and a power of 90%. Published data indicated the standard deviation in the primary end-point (Hb increase) to be approximately 20 g/L. Published data also suggested the smallest clinically relevant difference to be 15–20 g/L.The sample size calculation was therefore focused on the smaller value (15 g/L). Based on the above assumptions, a two-sample *t*-test showed that 39 patients per group were needed (78 in total). To adjust for withdrawals and the possibility of using a non-parametric method in the analysis, 45 patients per group were planned for randomization [4,6,11].

Treatment allocation

Patients were allocated to any of the treatments over the Internet, by applying the minimization method to ensure a balance within the patient factors age, B-Hb and S-ferritin [16].

Blinding

Venofer® is a dark-brown, non-transparent, aqueous solution to be administered intravenously. There is no placebo solution available. The primary end-point was a laboratory value, and the analyses did not include any subjective evaluations. The dosing schedules were independent of a follow-up of the primary end-point. The final assessments were done from computerized information only. For these reasons the study was regarded as observer-blind.

Statistical methods

The primary analyses were applicable to all patients who, after randomization, received at least one dose and had at least one value registered in the primary efficacy variable. The last observation carried forward (LOCF) approach was used as an imputation method, in the even of the patient withdrawing from the study because of intolerance.

Study compliance

The study was conducted in compliance with the current issue of the Declaration of Helsinki, Good Clinical Practice Guidelines (GCP, CPMP/ICH/135/9) and the Swedish regulatory requirements. The study was approved by the Ethics Committee of Lund University and the local Ethics Committees (Lu 414-03, 10 November 2003). No significant protocol deviations occurred during the study.

Results

Doses administered

The mean dose ($\pm$SD) given to all patients was 1.708 ± 331 mg in the i.v. iron group. Nine patients (20%), most of whom needed more than the average dose, received i.v. iron once weekly during the first 8–10 weeks, while the majority of the patients had i.v. iron every second week. The oral iron group received 38.387 ± 19.955 mg, indicating that the mean i.v. iron dose was only about 4% of the oral iron dose. Both dose regimens followed the recommendations of the SPC.

Patient flow

The completion of treatment is outlined in Figure 1. In the i.v. iron group, 43/45 randomized patients completed the study: 1 patient had a temporary stop because of increased IBD symptoms, 1 patient was withdrawn owing to abdominal carcinoma and 1 patient was withdrawn on day 29 because of thrombocytopenia. The safety board judged the last of these events as "possibly related" to ongoing treatment. In the oral iron group, 11 patients (24%) were withdrawn because of intolerance to the prescribed oral treatment. The intolerance to the iron

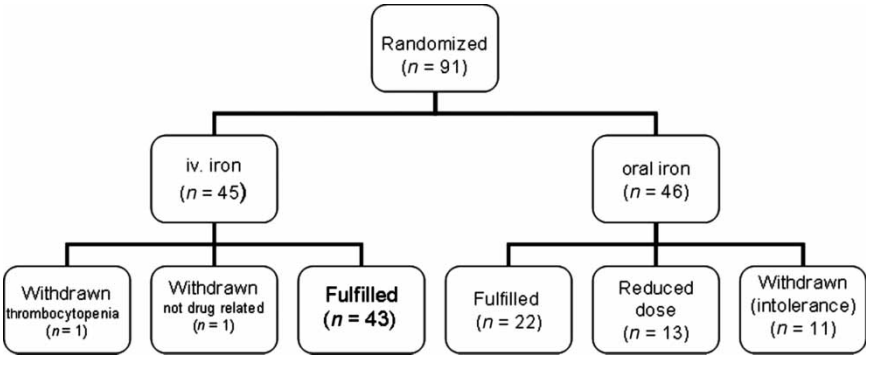

Figure 1. Fulfilment of treatment.

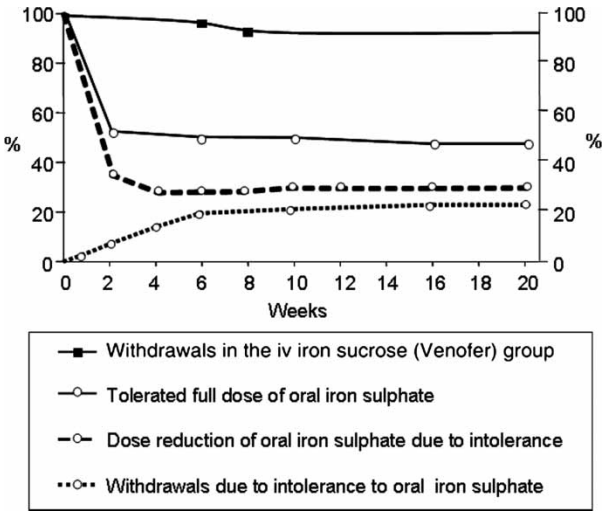

Figure 2. Time sequence of withdrawals and dose reductions.

tablets occurred mainly in the early stage of the treatment, as shown in Figure 2, resulting in either withdrawal from the study or dose reduction (28% of patients). Concerning tolerability, the statistical analysis shows a clear advantage in the group using i.v. iron ($p = 0.0009$). The intolerances reported are described under the section, "Adverse reactions".

Haemoglobin increase

Figure 3 shows the haemoglobin increase during treatment, as a result of the two different regimens. For those, who did not tolerate oral iron (24% of the patients) the Hb increase was less satisfactory (Figure 4).

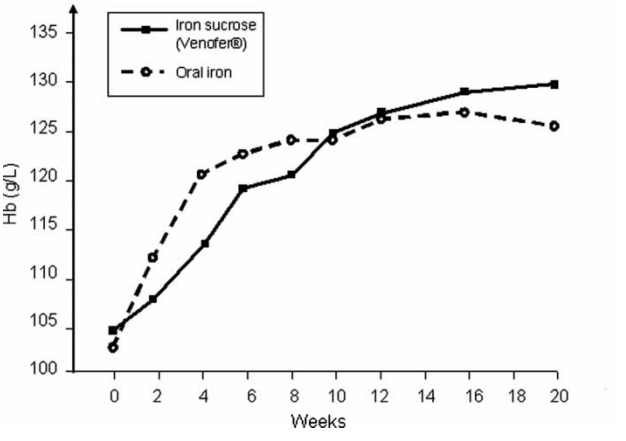

Figure 3. Haemoglobin increase in patients with anaemia and IBD. The mean B-Hb concentration during treatment (ITT = intention to treat analysis and LOCF = last observation carried forward). I.v. iron group $n = 45$; oral iron group $n = 46$.

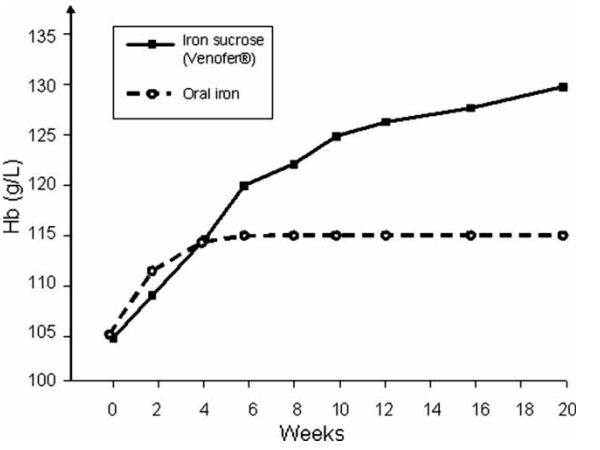

Figure 4. Mean haemoglobin response in patients with anaemia and inflammatory bowel disease (IBD). Patients treated with iron sucrose (all tolerant) compared to those who withdrew ($n = 11$) from oral iron sulphate because of intolerance (ITT = intention to treat analysis and LOCF = last observation carried forward).

In the i.v. iron group there was no significant difference in haemoglobin response between those given iron every week or every second week.

Changes in B-Hb after 20 weeks (EOT)

Only 47% of the patients in the oral iron group responded with an increase in B-Hb of >20 g/L despite treatment with the maximal tolerated and approved dose of iron sulphate. In the i.v. iron group, 66% of the patients responded correspondingly ($p = 0.07$). This is in agreement with remaining anaemia at EOT and is also reflected by the proportion of patients reaching the mean reference Hb concentration (males 150 g/L and females 130 g/L) (Figure 5).

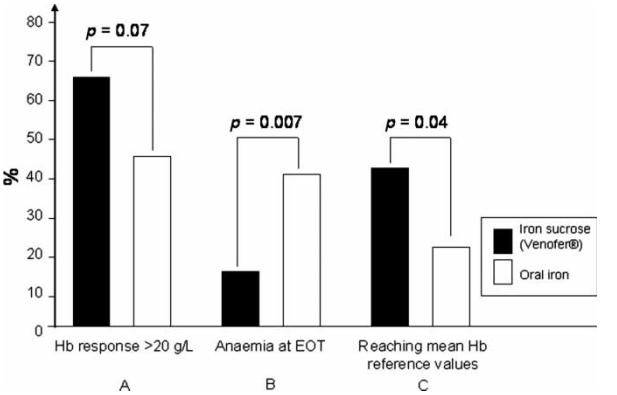

Figure 5. Proportion of patients with Hb response ≥20 g/L (A), anaemia at end of treatment (EOT) (B), reaching mean Hb for a healthy population (C).

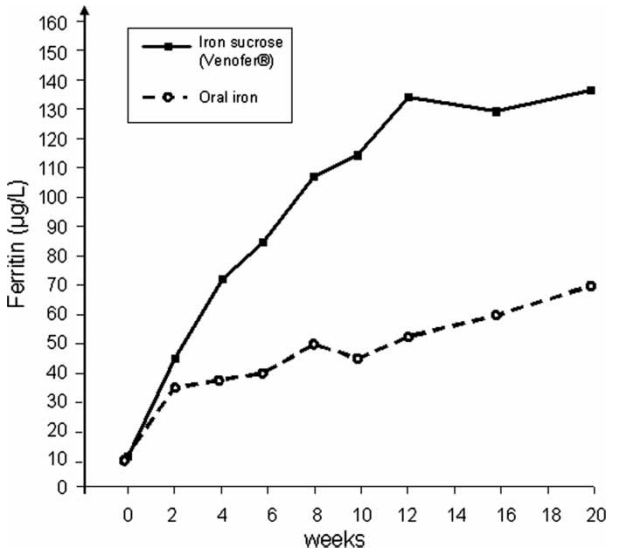

Figure 6. Mean levels of S-ferritin in the oral ($n=46$) and i.v. ($n=45$) iron groups. Last observation carried forward (LOCF) during the study period.

Iron stores after 20 weeks (EOT)

There was a significant difference in S-ferritin during treatment between the two groups. At EOT, S-ferritin increased significantly more in the intravenous compared with the oral iron group ($p=0.001$) (Figure 6). In parallel, other parameters of iron status improved; e.g. mean serum transferrin receptor, which initially was increased, decreased to normal on treatment with i.v. iron. In the oral iron group the values also decreased but with a wider range (data not shown).

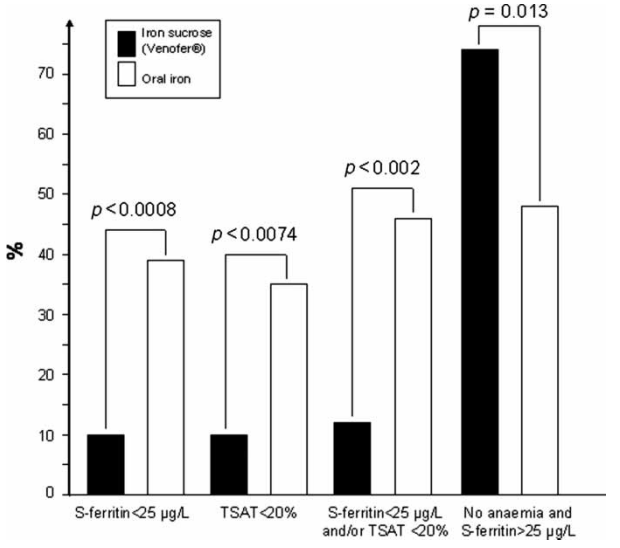

Figure 7. Proportion of patients with iron deficiency at end of treatment (EOT) (week 20) and proportion of patients without anaemia and normal S-ferritin concentrations (>25 µg/L).

At EOT there was a clear difference between the groups regarding remaining iron deficiency as indicated by S-ferritin and TSAT. In the i.v. iron group, 74% of the patients had no anaemia combined with normal S-ferritin (>25 µg/L) at EOT, compared with 48% in the oral iron group ($p<0.013$) (Figure 7).

Disease activity index

HBAI scores for CD and WI for UC were low at the start of the study (see Table I). The disease activity was largely unchanged by intravenous and oral iron treatment (data not shown).

Adverse reactions

One serious AE occurred during the study. One male patient suffered from thrombocytopenia of unclear origin, resulting in a "possible" causality evaluation towards iron sucrose. The adverse reactions which occurred more than once in each treatment arm are listed in Table IV. The adverse reactions seen on oral iron were dominated by gastrointestinal symptoms. Rigor described by two patients receiving iron sucrose was stiffness of the legs following treatment.

Discussion

This study shows that less than half of the patients tolerated the full oral dose recommended by the manufacturer and 24% discontinued the treatment because of intolerance. Consequently, only 28% of the patients receiving oral iron reached the recommended S-ferritin target (>100 µg/L). In contrast, all patients who received iron sucrose tolerated the treatment. Accordingly, a striking difference in S-ferritin concentrations was observed following treatment with intravenous compared with oral iron. In fact, treatment with i.v. iron sucrose gave a significantly higher S-ferritin concentration despite the suboptimal dose used. Since a maximal tolerated dose of oral iron was used, the total amount of iron

Table IV. Adverse reactions occurring more than once in each group.

Adverse reaction	I.v. iron sucrose	Oral iron sulphate
Abdominal pain		11
Diarrhoea		9
Melaena		2
Nausea		3
Vomiting		3
Headache	2	
Rigors	3	

given orally was 20 times higher than the dose given intravenously. This effective restoration of iron stores by i.v. iron sucrose is reflected by a more pronounced change in haemoglobin, a higher proportion of patients reaching their mean reference Hb concentration and fewer patients remaining anaemic at the end of the study (EOT).

The definitions of iron deficiency and anaemia are key considerations. Since anaemia is a rather late secondary result of iron deficiency, the early signals for the threat of anaemia in IBD will depend on iron parameters. Several of them are in use, but there seems to be consensus that S-ferritin constitutes the optimal measurement as a compromise between simplicity, availability, sensitivity and specificity for iron deficiency [3].

For some time now, oral iron has been the traditional treatment for anaemia in IBD, since it is cheap, readily available and recommended by various guidelines, e.g. by the British Society of Gastroenterology [17]. Recently, a European group developed guidelines on diagnosis and management of iron deficiency and anaemia in IBD [18]. Although they concluded that the preferred route of iron supplementation in IBD is intravenous, the guidelines still suggest a place for oral iron supplementation in IBD, where absolute indications for intravenous iron therapy are not met [18]. Since gastrointestinal adverse effects such as nausea, bloating, diarrhoea and gastrointestinal pain are the most common reasons for discontinuation of the treatment with oral iron, these symptoms can be more pronounced in IBD patients. Although not controlled for, we found that patients with previous experience of severe side effects from oral iron were more likely to refuse participation in this study.

Furthermore, in contrast to treatment with i.v. iron sucrose, oral iron has also been found to cause disease exacerbation in clinical practice [19]. This is supported by rodent models where oral iron supplementation resulted in aggravated oxidative stress and inflammatory disease activity and even the development of colorectal cancer (for a review, see Kulnigg & Gasché [20]). Despite these findings, oral iron has been the treatment of choice since i.v. iron has been unavailable or has carried a risk of serious adverse reactions, particularly in relation to earlier i.v. iron parenteral formulations like iron dextran. However, ever since the introduction of i.v. iron sucrose in 1950, a consistent safety record has been compiled [9,21–23].

A cautious calculation of the iron utilized following the two treatments, based on the mean increase of B-haemoglobin and S-ferritin, shows that about 1–2% of the oral iron was absorbed and utilized compared with 100% of the i.v. iron sucrose. This is in agreement with previous pharmacokinetic and pharmacodynamic studies [24]. The non-absorbed oral iron passes the gastrointestinal tract, where it can affect the mucosa and aggravate the disease [19]. Furthermore, most of the patients were receiving immunosuppressives or other medication, which could further interfere with iron absorption. Even after 5 months of treatment with oral iron, about 40% of the patients in our study were still both iron deficient and anaemic.

The recent discovery of hepcidin as an iron-regulating hormone has also contributed towards explaining why oral iron supplementation is not effective in many patients with anaemia and inflammation [25]. It has been demonstrated that subjects with active CD have elevated Il-6 levels and elevated hepcidin production, indicating that oral iron may be of limited benefit [26].

Iron sucrose was given once weekly or every other week until the total dose was reached. Still, some patients were anaemic at EOT. There are several possible explanations for this. The Ganzoni formula [12] for calculation of the dose may underestimate the therapeutic dose, particularly in severely anaemic patients, or in patients who lost iron in the gastrointestinal tract because of inflammation and bleeding or had very low endogenous erythropoietin (EPO) production.

The use of EPO has provided an alternative treatment for anaemia. However, adverse reactions from EPO and its high cost have called its prominent place in therapy into question, and a number of studies have shown that i.v. iron alone is very effective against anaemia, particularly since many patients with IBD and anaemia have increased endogenous S-EPO levels [27]. Therefore EPO treatment seems to be indicated only when i.v. iron treatment alone is insufficient, which may occur in only 20% of patients with IBD [8], or when the endogenous EPO production is low. A reasonable strategy might be to estimate the ferritin response to treatment, to give additional iron sucrose when ferritin is subnormal and to add EPO when there is no adequate response to treatment despite normalized S-ferritin.

In conclusion, the results of this randomized, controlled, open-label, multicentre study show that i.v. iron sucrose treatment is superior to oral iron in correcting haemoglobin and iron stores. The data show that iron sucrose has a better gastrointestinal safety record, which resulted in much better tolerance of iron sucrose than of oral iron. However, the optimal dose for correction and maintaining target haemoglobin levels and iron stores still remains to be established in anaemia of IBD.

Acknowledgements

The study was supported by Renapharma AB, Uppsala, Sweden.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Cronin C, Shanahan F. Anemia in patients with chronic inflammatory bowel disease. Am J Gastroenterol 2001;96: 2296–8.
[2] Gasché C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. Gut 2004;53:1190–7.
[3] Guagnozzi D, Severi C, Ialongo P, Viscido A, Patrizi F, Testino G, et al. Ferritin as a simple indicator of iron deficiency in anemic IBD patients. Inflam Bowel Dis 2006; 12:150–1.
[4] Gasché C, Dejaco C, Waldhoer T, Tillinger W, Rainisch W, Fueger GF, et al. Intravenous iron and erythropoietin for anemia associated with Crohn disease. Ann Int Med 1997; 126:782–7.
[5] Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflam Bowel Dis 2006;12:123–30.
[6] Gasché C, Dejaco C, Reinisch W, Tillinger W, Waldhoer T, Fueger GF, et al. Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoietin. Digestion 1999;60:262–7.
[7] Gasché C, Waldhoer T, Feichtenschlager T, Male C, Mayer A, Mittermaier C, et al. Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. Am J Gastroenterol 2001;96:2382–7.
[8] Bodemar G, Kechagias S, Almer S, Danielson BG. Treatment of anaemia in inflammatory bowel disease with iron sucrose. Scand J Gastroenterol 2004;39:454–8.
[9] Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. Nephrol Dial Transplant 2005;20:1443–9.
[10] Van Wyck DB, Cavallo G, Spinowitz BS, Adhikarla R, Gagnon S, Charytan C, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American Clinical Trial. Am J Kidney Dis 2000;36:88–97.
[11] Schröder O, Mickisch O, Seidler U, de Weerth A, Dignass AU, Herfarth H, 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;100:2503–9.
[12] Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweiz Med Wochenschrift 1970;100:301–3.
[13] Skjelbakken T, Langbakk B, Dahl IMS, Löchen M-L. Haemoglobin and anaemia in a gender perspective: The Tromsö Study. Eur J Haematol 2005;74:381–8.
[14] Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1:514.
[15] Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998;43:29–32.
[16] White SJ, Freedmann LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978;37: 849–57.
[17] Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. Gut 2000;46 Suppl 3-4:IV1–5 Erratum in: Gut 2000;47:872.
[18] Gasché C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel disease. Inflamm Bowel Dis 2007;13:1545–53.
[19] Erichsen K, Ulvik RJ, Nysaeter G, Johansen J, Ostborg J, Berstad A, et al. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. Scand J Gastroenterol 2005;40:1058–65.
[20] Kulnigg S, Gasché C. Systematic review: managing anaemia in Crohn's disease. Aliment Pharmacol Ther 2006;24: 1507–23.
[21] Yee J, Besarab A. Iron sucrose: the oldest iron therapy becomes new. Am J Kidney Dis 2002;40:1111–21.
[22] Besarab A, Frinak S, Yee J. An indistinct balance: the safety and efficacy of parenteral iron therapy. J Am Soc Nephrol 1999;10:2029–43.
[23] Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378–82.
[24] Danielson BG, Beshara S. Pharmacokinetics and utilization of iron sucrose. Am J Kidney Dis 2003;42:1104.
[25] Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. Am J Physiol GI 2005;290:199–203.
[26] Semrin G, Fishman DS, Bousvaros A, Zholudev A, Saunders AC, Correia CE, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. Inflam Bowel Dis 2006;12: 1101–6.
[27] Gasché C, Reinisch W, Lochs H, Parsaei B, Bakos S, Wyatt J, et al. Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. Digestive Dis Sci 1994;39:1930–4.