

# Rapid Recurrence of IBD-Associated Anemia and Iron Deficiency After Intravenous Iron Sucrose and Erythropoietin Treatment

Stefanie Kulnigg, MD<sup>1</sup>, Lena Teischinger<sup>1</sup>, Clemens Dejaco, MD<sup>1</sup>, Thomas Waldhör, PhD<sup>2</sup> and Christoph Gasche, MD<sup>1,3</sup>

- OBJECTIVES:** Anemia is a common complication of inflammatory bowel disease (IBD) and iron deficiency (ID) is its predominant cause. Therefore, oral and intravenous iron replacements are widely used. This study was performed to evaluate the frequency and timing of anemia and ID recurrence after a successful treatment cycle.
- METHODS:** Medical records of patients who had received iron sucrose with or without erythropoietin (EPO) in one of three prospective clinical trials that had been conducted at our center (*Ann Intern Med* 1997, *Digestion* 1999, and *Am J Gastroenterol* 2001) were analyzed for a 5-year follow-up period. The risk for recurrence of anemia (hemoglobin (Hb) < 12/13 g per 100 ml) and ID (ferritin < 30 µg/l) was evaluated by Kaplan–Meier analysis using the log-rank test.
- RESULTS:** Eighty-eight patients were available for analysis. Patients had received a mean iron dose of 2,500 mg (range 600–3,600 mg); 33 (37.1%) patients had also received EPO. Anemia recurred in a median of 10 months (95% confidence interval (CI) 8–12) and ID recurred within 19 months (95% CI 11–28). The iron dose had no influence on recurrence of ID or anemia. ID (but not anemia) recurred faster in patients with a post-treatment ferritin level < 100 µg/l (median 4 months, 95% CI 1–7) than in patients with ferritin level between 100 and 400 µg/l (median 11 months, 95% CI 6–16) and >400 µg/l (median 49 months, 95% CI 32–66; *P* < 0.001).
- CONCLUSIONS:** IBD-associated ID and anemia recur surprisingly fast, indicating that maintenance treatment may be needed in a portion of the patient population. Recurrence of ID (but not anemia) can be delayed by aiming for high post-treatment ferritin levels.

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## INTRODUCTION

Anemia is a common complication of inflammatory bowel disease (IBD) affecting about one-third of patients (1). Iron deficiency (ID) is the most frequent cause of anemia in IBD. ID results not only from continuous or recurrent blood loss through ulcerations of the bowel mucosa, but also from decreased iron intake or limited absorption. This may lead to a negative iron balance and iron deficiency anemia. In chronic inflammatory diseases such as rheumatoid arthritis or IBD, increased cytokine levels, including interleukin-

1, interleukin-6, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ , may suppress erythropoiesis (directly and through inhibition of erythropoietin (EPO) production) and cause iron withholding in the reticuloendothelial system through hepcidin (2). The resulting condition is termed as anemia of chronic disease, which is also present in IBD and is usually coincident with ID. Anemia-specific symptoms such as headache, dizziness, palpitations, and shortness of breath and ID-associated symptoms such as impaired nail growth, skin defects, sleeping disorders, loss of libido, and erectile dysfunction

<sup>1</sup>Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria; <sup>2</sup>Department of Epidemiology, Center for Public Health, Medical University of Vienna, Vienna, Austria; <sup>3</sup>Christian Doppler Laboratory on Molecular Cancer Chemoprevention, Medical University of Vienna, Vienna, Austria. **Correspondence:** Christoph Gasche, MD, Abteilung für Gastroenterologie und Hepatologie, Währinger Gürtel 18-20, Vienna A-1090, Austria. E-mail: christoph.gasche@meduniwien.ac.at

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are associated with a decreased quality of life, reduced ability to work, and in severe cases with hospitalization or prolongation of hospital stays. Prevention, early detection, and appropriate treatment of ID and anemia are important goals in the management of IBD.

In IBD, intravenous iron preparations are considered the preferred route of iron supplementation (3). Absolute indications for intravenous iron include severe anemia (hemoglobin (Hb) < 10 g per 100 ml), intolerance, or inappropriate response to oral iron, severe intestinal disease activity, concomitant therapy with an erythropoiesis-stimulating agent, or patient preference. Modern intravenous iron preparations are safe, effective (1,4), and can refill iron stores fast. In IBD, most studies were conducted with intravenous iron sucrose (1). In patients who do not respond or have only a partial response to intravenous iron, the addition of an erythropoiesis-stimulating agent can normalize Hb levels in up to 100% of patients (5–10), indicating that anemia and ID can be effectively managed by appropriate therapy. However, no data are available on the short- and long-term outcomes after anemia treatment. This study was conducted to evaluate the frequency and timing of recurring anemia and ID after a successful treatment cycle with iron sucrose, with or without additional EPO. We hypothesized that the recurrence inversely relates to the amount of iron infused and the post-treatment size of iron stores (as reflected by serum ferritin level).

## METHODS

This retrospective analysis was conducted at the Medical University of Vienna between June and September 2008. The local ethics committee approved the protocol. WHO criteria were used to define anemia (Hb < 12 g per 100 ml in non-pregnant females and < 13 g per 100 ml in males), ID was defined as serum ferritin < 30 µg/l in patients without clinical or biochemical evidence of inflammation, and < 100 µg/l in patients with active inflammation (3). As this was a retrospective analysis, the presence of clinical disease activity was difficult to judge. Therefore, both cut offs were used for analysis.

### Patients

Patients who had participated in one of three prospective clinical trials (9,11,12) each testing the efficacy of iron sucrose with or without EPO for the treatment of anemia in IBD were included into this analysis. In all studies, patients with Hb ≤ 10.5 g per 100 ml were included and response was defined as Hb increase > 2 g per 100 ml. The exact study design has been described elsewhere (9,11,12). In brief:

- (1) In the single-center Crohn study (9), 40 patients with anemia and Crohn's disease (CD) had received up to 3,600 mg intravenous iron sucrose within 16 weeks. In addition to iron treatment patients had been randomized to treatment with either placebo or EPO at a 1:1 ratio during the first 8 weeks of the study. In the second part of the study, non-responders received concomitant EPO

treatment, whereas responders were continued on iron sucrose only. Treatment had been stopped prematurely in patients who had reached an Hb concentration > 14.0 g per 100 ml before the end of the blinded phase.

- (2) In the single-center Colitis study (11), 20 ulcerative colitis (UC) patients were treated with 2,000 mg iron sucrose for 8 weeks. Partial responders (increase in Hb ≥ 2 g per 100 ml but Hb ≤ 10.5 g per 100 ml) were continued on iron sucrose only, whereas EPO was added in non-responders.
- (3) In the multi-center Predict study (12), 103 patients with either CD or UC were treated with 1,200 mg iron sucrose for 4 weeks. Non-responders or partial responders received EPO and iron sucrose according to the investigator's clinical judgment. A subgroup of 29 patients (8 UC, 21 CD) was treated at the Medical University of Vienna and was available for analysis.

### Data collection

Laboratory and clinical data were obtained from case report forms and medical records, starting at study end for a maximum follow-up period of 5 years. Laboratory data included complete blood count and iron parameters (transferrin, transferrin saturation (TfS), serum iron, and serum ferritin). Patients without complete blood count and iron status within the first 3 months after the end of iron replacement therapy (IRT) were excluded from analysis. If follow-up data (complete blood count or iron status) were not available for more than 6 months, the patient was considered lost to follow-up. Values for Hb, serum ferritin, and TfS at the end of IRT (= first data point of this study) were taken from the last scheduled study visit within the Crohn, Colitis, or Predict study. Primary end points were time until Hb dropped to < 12/13 g per 100 ml, ferritin to < 30 or < 100 µg/l, TfS < 16%, and time until iron re-treatment.

### Statistical analysis

Descriptive statistics were applied to describe the study cohort. For comparison of characteristics within the study populations, one-way ANOVA was used. Time to meet certain criteria was analyzed by Kaplan–Meier analysis using the log-rank test. In case of multiple comparisons, Bonferroni-corrected significance levels were used. If patients were lost to follow-up they were censored for the Kaplan–Meier analysis. A value of  $P < 0.05$  was considered to be statistically significant. SPSS software (Version 15.0, SPSS Inc., Chicago, IL) was used.

## RESULTS

### Patients' characteristics after IRT

A total of 88 patients ( $n = 39$  from Crohn study,  $n = 20$  from Colitis study,  $n = 29$  from Predict study) were available for analysis; one patient from the Crohn study did not receive any study medication and was therefore excluded from analysis. Data for complete blood count were available for a median of

27 months (95% CI 25–35 months), and for iron parameters for 20 months (95% CI 21–30 months). Studies did not differ in age, Hb, and serum ferritin before IRT. Differences, however, were identified for gender, subtype of IBD, total iron dose, EPO treatment, and TfS (Table 1). Patients received a mean iron dose of 2,500 mg (range 600–3,600 mg). Thirty-three patients (37.1%) also received EPO. The highest iron dose was given in the Crohn trial, followed by the Colitis and the Predict study. At the end of IRT, levels of Hb were higher in the Crohn study, again followed by the Colitis and the Predict study ( $P < 0.001$ ). This was also true for serum ferritin and TfS ( $P < 0.001$ ).

After IRT, 56 patients (63.6%) had Hb levels  $\geq$  normal, 84 (95.5%) had serum ferritin  $\geq 30 \mu\text{g/l}$ , 76 (86.4%) ferritin  $\geq 100 \mu\text{g/l}$ , and 41 patients (47.1%) had TfS  $\geq 16\%$  (Table 2). Of patients with normal hemoglobin, 2 (3.6%) had ferritin levels  $< 30 \mu\text{g/l}$ , 2 (3.6%) between 30 and  $100 \mu\text{g/l}$ , and 52 (92.9%) had ferritin levels  $> 100 \mu\text{g/l}$ . Twenty-two patients (39.3%) had TfS  $< 16\%$ . Of anemic patients, 2 (6.25%) had ferritin levels  $< 30 \mu\text{g/l}$ , 6 (18.75%) between 30 and  $100 \mu\text{g/l}$ , and 24 (75%) had ferritin levels  $> 100 \mu\text{g/l}$ . Twenty-four patients (75%) had TfS  $< 16\%$ . In 34 patients (38.7%) all parameters were within the normal range (Crohn study  $n = 25/62.5\%$ , Colitis study  $n = 5/25\%$ , Predict study  $n = 4/13.8\%$ ).

**Recurrence of anemia and ID after iron replacement therapy**

Only patients who had reached normal levels for a certain parameter were analyzed for this parameter (e.g., a patient with normal Hb but low TfS was analyzed for time until Hb drops below normal but not for TfS below 16%). Anemia recurred in 50% of patients after 10 months (95% CI 8–12 months). The median time until the serum ferritin dropped to  $< 30 \mu\text{g/l}$  was 19 months (95% CI 11–28 months), until the serum ferritin dropped to  $< 100 \mu\text{g/l}$  was 11 months (95% CI 8–14), and until the TfS dropped to  $< 16\%$  was 6 months (95% CI 0–13) (Table 3, Figure 1). The fastest recurrence for Hb and serum ferritin was observed in the Colitis study, and for TfS in the Predict study. Iron re-treatment was initiated within a median of 16 months (95% CI 7–24).

Subgroup analysis (EPO treatment, gender, subtype of IBD) revealed no difference for anemia recurrence, iron re-treatment, or time until TfS dropped below normal. However, severe ID (ferritin  $< 30 \mu\text{g/l}$ ) recurred faster in patients without concomitant EPO treatment and UC, and moderate ID (ferritin  $< 100 \mu\text{g/l}$ ) faster in male patients and UC (Table 4).

As the iron dosage varied within and between studies, patients were further analyzed according to their actually administered iron dosage. Twenty-four patients (27.3%) received 600–1,200 mg (referred to as the “1,200 mg group”), 21 (23.6%) 1,201–2,000 mg (referred to as the “2,000 mg group”), and 53 (48.3%) 2,001–3,600 mg (referred to as the “3,600 mg group”). No difference in Hb and serum ferritin was observed before IRT (Table 5). The 1,200 mg group had significantly lower Hb levels after IRT than the 2,000 mg or 3,600 mg group ( $P < 0.001$ ). Also, serum ferritin and TfS after IRT were highest in the 3,600 mg

**Table 1. Patient characteristics before and after iron replacement therapy**

	n	CD n (%)	Age (years)	Female n (%)	Total iron dose (mg)	EPO n (%)	Hb (g per 100 ml)		Ferritin ( $\mu\text{g/l}$ )		Transferrin saturation (%)	
							Before IRT	After IRT	Before IRT	After IRT	Before IRT	After IRT
Crohn study	39	39 (100)	32 (28–36)	26 (66.7)	3400 (3200–3600)	24 (60.0)	8.6 (8.1–9)	13.4 (13–13.8)	23 (10–36)	688 (542–833)	4.2 (2.6–5.9)	25.7 (22–30)
Colitis study	20	0 (0)	36 (30–41)	6 (30.0)	2300 (2000–2600)	4 (20.0)	8.3 (7.7–8.9)	12.7 (12–13.4)	18 (0–40)	330 (124–537)	3.9 (1–7)	15.8 (9–23)
Predict study	29	21 (72)	32 (28–36)	21 (72.4)	1300 (1200–1400)	5 (17.2)	9.1 (8.6–9.6)	11.9 (11.4–12.4)	47 (10–84)	266 (192–341)	14.1 (5–23)	11 (8–13)
Combined	88	60 (68)	33 (30–35)	53 (59.6)	2500 (2200–2700)	33 (37.1)	8.7 (8.4–9)	12.7 (12.4–13.1)	29 (16–43)	468 (377–558)	5.2 (3.6–6.9)	18.6 (16–21)
P value		$< 0.001$	0.512	0.07	$< 0.001$	$< 0.001$	0.129	$< 0.001$	0.207	$< 0.001$	$< 0.001$	$< 0.001$

CD, Crohn's disease; EPO, erythropoietin; Hb, hemoglobin; IRT, iron replacement therapy. Data are presented as mean (95% CI).

**Table 2.** Number (%) of patients with normal levels of hemoglobin, serum ferritin, or transferrin saturation after iron replacement therapy

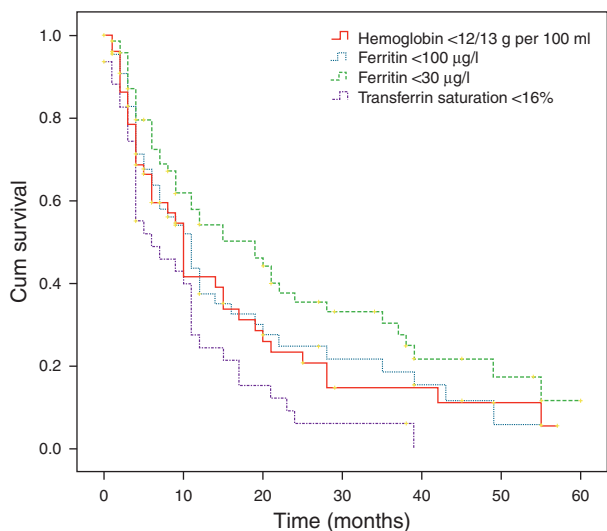
	Hb $\geq$ 12/13 g per 100 ml	Ferritin $\geq$ 100 $\mu$ g/l	Ferritin $\geq$ 30 $\mu$ g/l	TfS $\geq$ 16%
Crohn study	31 (79.5)	37 (94.9)	39 (97.5)	30 (76.9)
Colitis study	14 (70.0)	14 (70.0)	16 (80.0)	6 (30.0)
Predict study	11 (37.9)	25 (86.2)	29 (100.0)	5 (17.9)
Combined	56 (63.6)	76 (86.4)	84 (95.5)	41 (47.1)

Hb, hemoglobin; TfS, transferrin saturation.  
Data are presented as *n* (%).

**Table 3.** Time (months) until hemoglobin, serum ferritin, and transferrin saturation dropped below certain cutoff levels

Median (95% CI)	Hb $<$ 12/13 g per 100 ml	Ferritin $<$ 100 $\mu$ g/l	Ferritin $<$ 30 $\mu$ g/l	TfS $<$ 16%
Crohn's study	10 (9–11)	16 (5–27)	20 (13–27)	6 (4–8)
Colitis study	6 (0–14)	4 (3–5)	4 (0–19)	12 (4–20)
Predict study	14 (6–22)	7 (5–8)	11 (5–17)	3 (0–7)
Combined	10 (8–12)	11 (8–14)	19 (11–28)	6 (0–13)

CI, confidence interval; Hb, hemoglobin; TfS, transferrin saturation.  
Data are presented as median (95% CI).

**Figure 1.** Recurrence of anemia and iron deficiency. Kaplan–Meier analyses were performed for the time until hemoglobin (Hb) dropped to  $<$ 12/13 g per 100 ml, ferritin dropped to  $<$ 30  $\mu$ g/l, transferrin saturation (TfS) to  $<$ 16%, or time until iron re-treatment. Anemia recurred within a median of 10 months with up to 80% of patients having subnormal Hb levels after 2 years. Ferritin dropped to  $<$ 100  $\mu$ g/l in a quite similar kinetic and to  $<$ 30  $\mu$ g/l somewhat slower. The fastest recurrence was observed for the transferrin saturation.

group. However, the total iron dosage had no influence on recurrence of anemia or ID, or start of iron re-treatment within the follow-up period (Figure 2a–d).

Patients were further analyzed, according to their serum ferritin level after IRT (reflecting iron stores). As serum ferritin levels after intravenous iron replacement overestimate the actual iron stores (13), patients were grouped into those with serum ferritin level  $<$ 100  $\mu$ g/l ( $n=12$ , 13.6%), between 100 and 400  $\mu$ g/l ( $n=41$ , 46.6%), and  $>$ 400  $\mu$ g/l ( $n=35$ , 39.8%). Patients with serum ferritin  $<$ 100  $\mu$ g/l had the lowest Hb after IRT (mean 11.4 g per 100 ml, 95% CI 10.4–12.4) compared with the other groups (100–400: mean 12.8 g per 100 ml, 95% CI 12.3–13.2, and  $>$ 400: 13.2 g per 100 ml, 95% CI 12.4–13,  $P=0.001$ ). In addition, the TfS was significantly higher in patients with serum ferritin levels  $>$ 400  $\mu$ g/l than in the other groups ( $>$ 400: mean 26.0%, 95% CI 21.1–30.9; 100–400: mean 14.7%, 95% CI 12.1–17.2;  $<$ 100: mean 10.5%, 95% CI 2.5–18.4,  $P<0.001$ ). However, no difference was observed in the median time until Hb and TfS dropped below normal (Figure 3a and c). The time until serum ferritin dropped to  $<$ 30  $\mu$ g/l was shorter in the group with serum ferritin levels  $<$ 100  $\mu$ g/l and 100–400  $\mu$ g/l ( $P<0.001$ , Figure 3b). The same is true when comparing the time until iron re-treatment between these groups ( $P<0.001$ , Figure 3d).

## DISCUSSION

Iron deficiency is the prevailing nutritional deficit in patients with IBD. Oral and intravenous replacement is the standard of care. Although oral iron therapy is typically maintained over years (if tolerated), intravenous replacement can be

**Table 4.** Time (months) until hemoglobin, serum ferritin, and transferrin saturation dropped below certain cutoff levels, sorted by concomitant EPO therapy, gender, or subtype of IBD

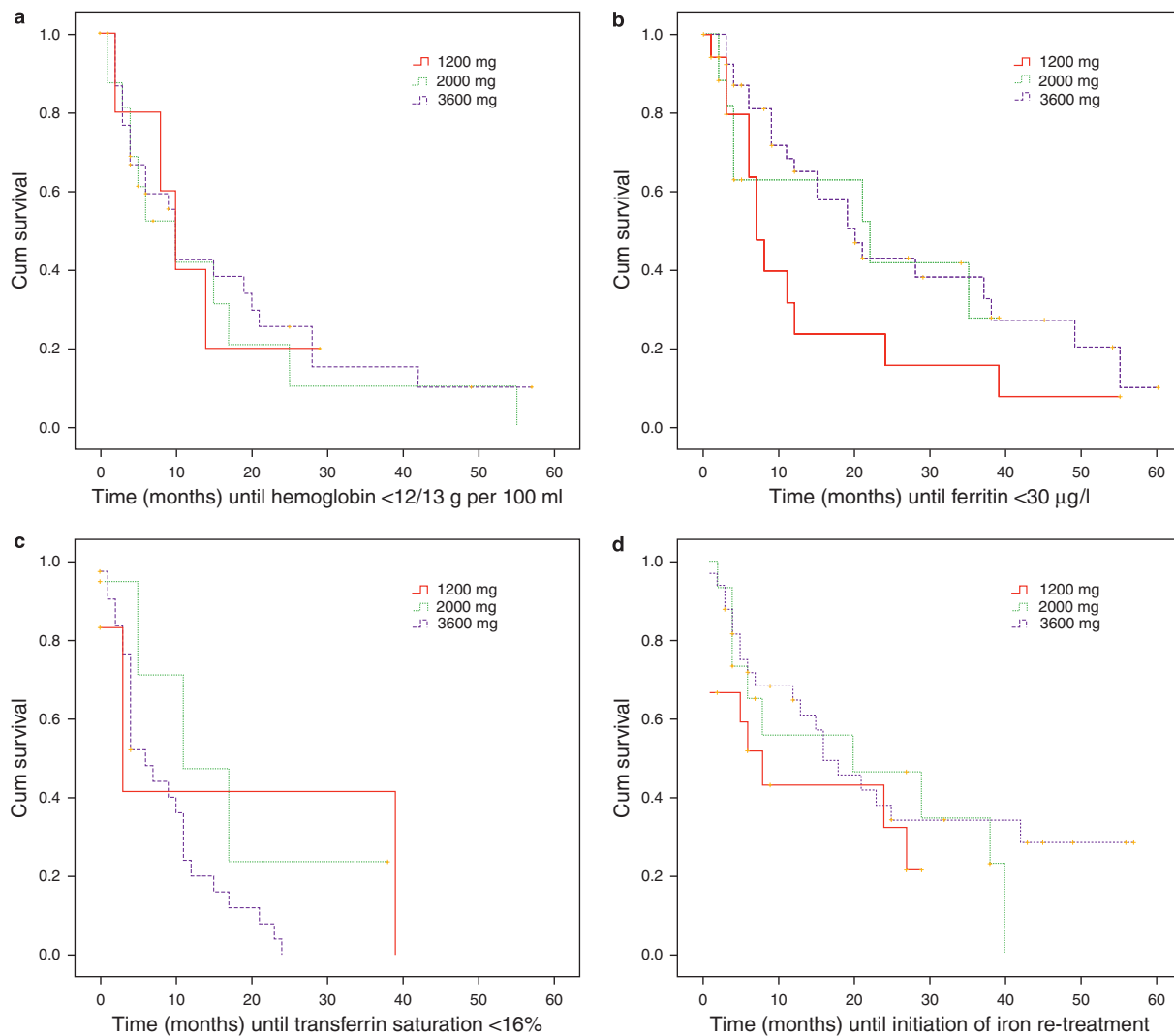
Median (95% CI)	Hb < 12/13 g per 100 ml	P	Ferritin < 100 µg/l	P	Ferritin < 30 µg/l	P	TfS < 16%	P	Iron retreatment	P
EPO	10 (5–15)	0.291	14 (6–22)	0.097	35 (16–54)	<b>0.048</b>	4 (0–7)	0.202	18 (4–32)	0.824
No EPO	10 (9–11)		6 (2–10)		9 (5–13)		10 (4–16)		15 (0–30)	
Female	8 (5–12)	0.627	14 (8–10)	<b>0.002</b>	20 (9–31)	0.063	10 (5–15)	0.943	18 (6–30)	0.598
Male	10 (3–17)		6 (4–8)		12 (5–20)		5 (3–7)		16 (11–21)	
CD	10 (9–11)	0.483	14 (9–19)	<b>&lt;0.001</b>	20 (13–27)	<b>0.026</b>	6 (4–8)	0.843	16 (1–31)	0.535
UC	8 (2–14)		4 (3–5)		7 (3–11)		12 (4–20)		20 (8–32)	

CD, Crohn's disease; CI, confidence interval; EPO, erythropoietin; Hb, hemoglobin; IBD, inflammatory bowel disease; TfS, transferrin saturation; UC, ulcerative colitis. Data are presented as n (%). Significant P values are in bold.

**Table 5.** Characteristics of patients sorted by administered iron dosage

n	CD, n (%)	Age (years)	Female, n (%)	Iron dose (mg)	EPO, n (%)	Hb (g per 100ml)		Ferritin (µg/l)		TfS (%)	
						Before IRT	After IRT	Before IRT	After IRT	Before IRT	After IRT
1200mg	24	17 (71)	18 (75)	1150 (1100–1200)	0 (0)	9.1 (8.5–9.7)	11.6 (11.2–12.1)	52 (11–93)	271 (183–358)	13.9 (2.5–25.4)	12 (9.1–14.8)
2000mg	21	4 (19)	9 (42.9)	2000 (1900–2000)	6 (28.6)	8.7 (8.1–9.3)	12.9 (12.3–13.5)	17 (0–40)	347 (153–541)	4 (0.9–7.1)	14.5 (8.1–20.8)
3600mg	43	39 (74)	26 (49.1)	3500 (3400–3600)	27 (50.9)	8.5 (8.0–8.9)	13.3 (12.8–13.7)	22 (10–34)	637 (496–777)	4.5 (2.8–6.1)	24.3 (20.3–28.2)
P value	<0.001	0.374	0.135	<0.001	<0.001	0.257	<0.001	0.106	<0.001	0.002	<0.001

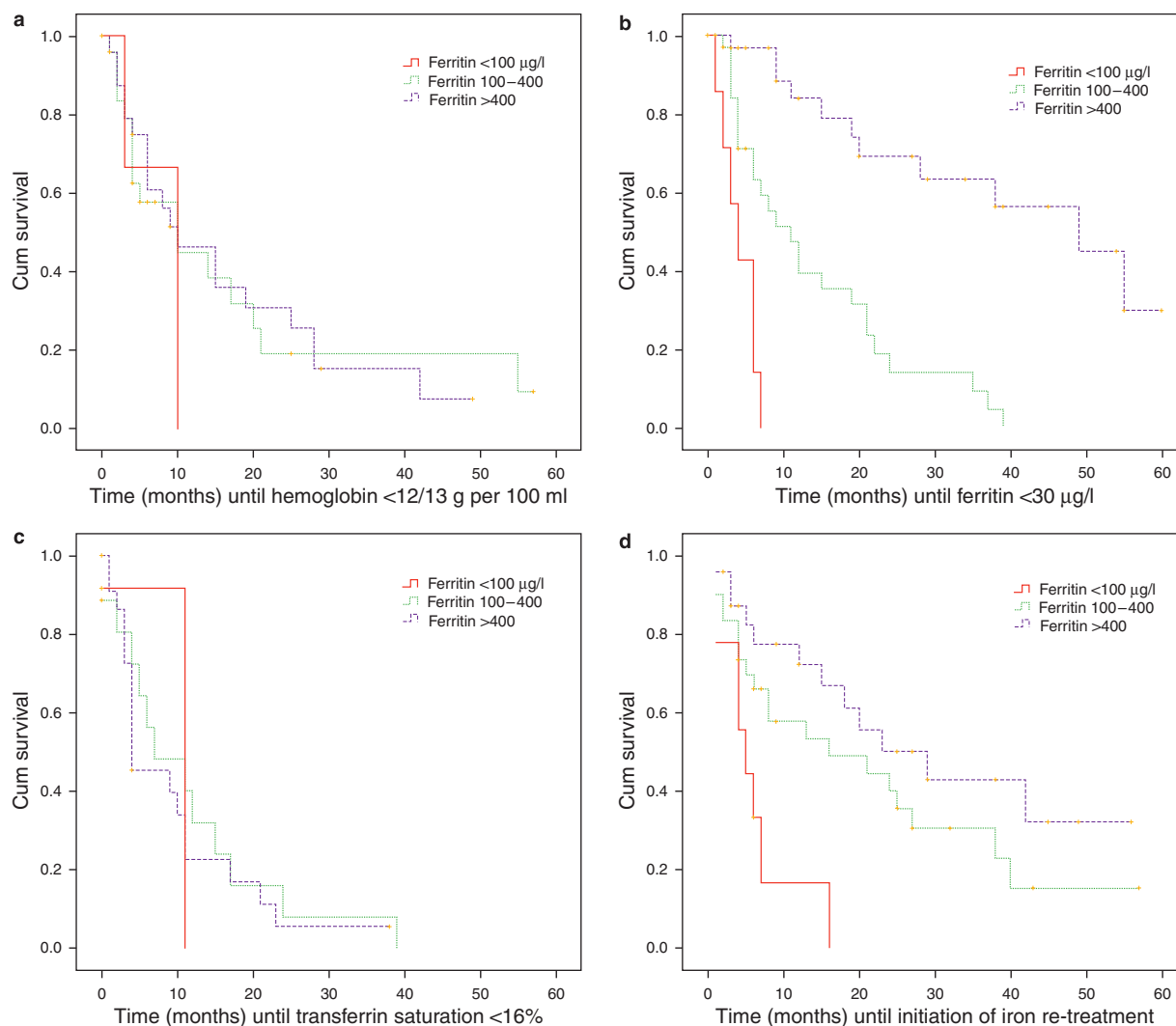
CD, Crohn's disease; EPO, erythropoietin; Hb, hemoglobin; IRT, iron replacement therapy; TfS, transferrin saturation. Data are presented as mean (95% CI).



**Figure 2.** Recurrence of anemia and iron deficiency according to iron dose. Kaplan–Meier analysis were performed until hemoglobin (Hb) dropped to <12/13 g per 100 ml (**a**), ferritin <30 µg/l (**b**), transferrin saturation (Tfs) <16% (**c**), and time until iron re-treatment (**d**), grouped by the total administered iron dosage (1,200 mg, 2,000 mg, 3,600 mg). The total iron dose did not affect recurrence of anemia, drop of transferrin saturation, or iron re-treatment. The lowest iron group (1,200 mg) showed significantly faster recurrence of iron deficiency (ferritin <30 µg/l) within 12 months  $P < 0.05$ . This effect was diluted in the analysis of the full 60-month follow-up period.

administered within weeks, specifically when considering single, high-dose infusions (e.g., 1,000 mg). So far the appropriate dosing of intravenous iron compounds is not well established. Ganzoni's formula (14) has been proposed for the estimation of the iron deficit, but it rather underestimates the problem in IBD (15) and is rarely used in clinical practice. When using iron sucrose, single doses between 200 and 300 mg are given once a week until a proper response is observed. However, on intravenous iron therapy the serum ferritin overestimates the bone marrow iron content and thus has its limitations for judging the sufficiency of iron replacement (13). For this study we hypothesized that the likelihood of anemia and ID recurrence relates to the initial iron dose and the post-treatment ferritin level.

Surprisingly, our data revealed a rapid recurrence: In 50% of patients anemia and ID (serum ferritin <100 µg/l) recurred within 10 and 11 months, respectively. The initial iron dose was associated with a better primary treatment success (**Table 2** shows higher response rates for the Crohn and the Colitis study, in which over 2,000 mg of iron had been given), but did not influence the rate of anemia recurrence and only the immediate recurrence of ID within the first year (**Figure 2b**). Post-treatment ferritin levels ranged between 9 and 1,920 µg/l and were in a direct relationship with the total amount of iron administered (**Table 5**). Lower ferritin levels were related to a faster recurrence of ID (**Figure 3b**), but again not to the recurrence of anemia (**Figure 3a**). Post-treatment serum ferritin levels of >400 µg/l



**Figure 3.** Recurrence of anemia and iron deficiency according to post-treatment serum ferritin levels. Kaplan–Meier analyses were performed for the time to hemoglobin (Hb) level  $<12/13$  g per 100 ml (a), ferritin level  $<30\mu\text{g/l}$  (b), transferrin saturation (TfS)  $<16\%$  (c), and iron re-treatment (d), grouped by serum ferritin levels after iron replacement therapy (IRT). No effect of the post-treatment ferritin levels was seen for the drop in Hb and transferrin saturation. Patients with low post-treatment ferritin levels, however, showed significant faster recurrence of iron deficiency (ferritin  $<30\mu\text{g/l}$ ) and needed earlier iron re-treatment.

prevented recurrence of ID within the following 1–5 years significantly better than any level below. Thus, intravenous iron replacement might want to target for ferritin levels of at least  $400\mu\text{g/l}$ . Concomitant EPO therapy, male gender and UC were associated with faster recurrence of ID. It is quite unexpected that male gender is a risk factor for recurrence of ID as females lose more iron through menstrual bleeding. In our studies, however, the primary iron replacement was not adjusted for body weight (as in Ganzoni’s formula), and thus it is likely that men received a lower iron dose per kilogram than women. This “under-treatment” could explain the faster recurrence of ID in males. Similarly, patients treated with EPO received a higher iron dose (EPO: mean  $3,200$  mg (95% CI  $2,900$ – $4,300$ ), no EPO:  $2,100$  mg

(95% CI  $1,800$ – $2,400$ ),  $P < 0.001$ ). Accordingly, patients with CD received more iron (CD: mean  $2,700$  mg (95% CI  $2,400$ – $3,000$ ), UC: mean  $2,000$  mg (95% CI  $1,700$ – $2,300$ ),  $P = 0.004$ ). We therefore believe that these characteristics are confounding variables of total iron dose influencing the recurrence of ID.

To the best of our knowledge this is the only study evaluating the long-term outcome after anemia treatment. Therefore our data cannot be compared with the existing literature. As for the retrospective nature of this study, several shortcomings have to be considered. Patient follow-up was irregular and incomplete. The best data were available for Hb levels. Clinical disease activity was difficult to judge from patient charts and reinitiation of iron therapy was at the physician’s personal

discretion. Therefore, we did not present data on clinical disease activity and the data on iron re-treatment have to be judged carefully. Furthermore, the three clinical trials that served as database for this analysis were performed in the pre-infliximab era. Changes in anti-inflammatory therapy may likely alter intestinal bleeding and thus recurrence of anemia and ID. On the other hand, the use of well-characterized study cohorts minimizes selection bias and ensures uniform inclusion criteria (e.g., baseline Hb) and predefined treatment regimen.

The higher the initial iron dose, the better was the initial treatment outcome. However, our data show that neither the iron dose nor post-treatment ferritin levels influenced the long-term results. It is possible that besides adequate control of inflammation, iron and/or EPO maintenance therapy is needed to prevent anemia recurrence in a significant subset of patients. To answer this question, a prospective, randomized trial for testing the effect of a regular maintenance therapy with intravenous iron has been initiated recently. The first results can be expected in 2 years. Until then, we may recommend aiming for a ferritin level of at least 400 µg/l at the end of intravenous iron replacement (with an upper safety limit of 800 µg/l to avoid iron overload) and regular follow-up of patients. The best indicator of recurrent ID has yet to be defined. Keeping ferritin levels high may be at least useful to prevent ID.

#### CONFLICT OF INTEREST

**Guarantor of the article:** Christoph Gasche, MD.

**Specific author contributions:** Stefanie Kulnigg contributed to the design of the study, collection and analysis of data, and wrote the manuscript. Lena Teischinger contributed to collection and analysis of data and editing of the manuscript. Clemens Dejaco contributed to collection of data and editing of the manuscript. Thomas Waldhoer contributed to statistical analysis and editing of the manuscript. Christoph Gasche contributed to design of the study, analysis of data, and editing of the manuscript. All authors approved the final version of the manuscript.

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## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Iron deficiency anemia is very common in inflammatory bowel diseases.
- ✓ Anemia has a great impact on quality of life.
- ✓ Standard treatment includes oral or intravenous iron with or without erythropoietin.

### WHAT IS NEW HERE

- ✓ After a successful treatment cycle, anemia recurred frequently and fast, indicating a need for maintenance therapy.
- ✓ Recurrence of iron deficiency is lower in patients with elevated post-treatment ferritin levels.

#### REFERENCES

1. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther* 2006;24:1507–23.
2. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. *Annu Rev Nutr* 2006;26:323–42.
3. Gasche C, Berstad A, Befrits R *et al*. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007;13:1545–53.
4. Gisbert JP, Gomollon F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol* 2008;103:1299–307.
5. Dohil R, Hassall E, Wadsworth LD *et al*. Recombinant human erythropoietin for treatment of anemia of chronic disease in children with Crohn's disease. *J Pediatr* 1998;132:155–9.
6. Horina JH, Petritsch W, Schmid CR *et al*. Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. *Gastroenterology* 1993;104:1828–31.
7. Gasche C, Reinisch W, Lochs H *et al*. Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. *Dig Dis Sci* 1994;39:1930–4.
8. Schreiber S, Howaldt S, Schnoor M *et al*. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996;334:619–23.
9. Gasche C, Dejaco C, Waldhoer T *et al*. Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. *1997;126:782–7*.
10. Koutroubakis IE, Karmiris K, Makreas S *et al*. Effectiveness of darbepoetin-alfa in combination with intravenous iron sucrose in patients with inflammatory bowel disease and refractory anaemia: a pilot study. *Eur J Gastroenterol Hepatol* 2006;18:421–5.
11. Gasche C, Dejaco C, Reinisch W *et al*. Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoietin. *Digestion* 1999;60:262–7.
12. Gasche C, Waldhoer T, Feichtenschlager T *et al*. Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. *Am J Gastroenterol* 2001;96:2382–7.
13. Ali M, Rigolosi R, Fayemi AO *et al*. Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. *Lancet* 1982;1:652–5.
14. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. *Schweiz Med Wochenschr* 1970;100:301–3.
15. 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;103:1182–92.