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Intravenous iron therapy restores functional iron deficiency induced by infliximab☆

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Abstract

Background and aims: Infliximab (IFX) and iron sucrose (FeS) are of high value in inflammatory bowel disease (IBD). We aimed to assess the relative role of both therapies in IBD related anaemia and their safety when used in combination.
Methods: IBD patients with anaemia receiving a first series of FeS infusions in addition to IFX were prospectively followed. We investigated serum kinetics of erythropoietin (EPO), soluble transferrin receptors (sTFRs) and vascular endothelial growth factor (VEGF).
Results: Data analysis included 87 patients of whom 49.4% achieved the target Hb level of 12.0 g/dL. IFX resulted in a significant increase of EPO and sTFR compared to baseline pre-IFX levels ($p=0.029$ and $p=0.005$ respectively) and after a 12-week combined FeS and IFX treatment, EPO and sTFR levels dropped significantly compared to pre-FeS levels ($p<0.001$ for both). Infusion related adverse events were recorded in 2 IFX treated patients (2.3%, 0.7% of the infusions) and were mild. Disease activity and quality of life were not affected.

Abbreviations: CDAI, Crohn's Disease Activity Index; CD, Crohn's disease; CRP, C-reactive protein; EPO, Erythropoietin; FeS, I.V. iron sucrose; Hb, Haemoglobin; IBD, Inflammatory Bowel Disease; IBDQ, Inflammatory Bowel Disease Questionnaire; IDRA, Iron deficiency related anaemia; IFX, Infliximab; I.V., intravenous; sTFR(s), soluble transferrin receptor (s); Tsat, Transferrin saturation; UC, Ulcerative Colitis; VEGF, Vascular endothelial growth factor (human).

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Conclusions: In anaemic IBD patients treated with IFX, combined administration of FeS is safe. Infliximab significantly increases serum EPO and sTFR levels resulting in an increased functional iron deficiency, which is restored after combined treatment with I.V. iron sucrose.

1. Introduction

Intravenous (I.V.) iron treatment is indicated for absolute and functional iron deficiency.[1] However, concerns have been raised with regards to the long-term and short-term safety of I.V. iron administered as iron dextrane, since it has been demonstrated that up to 26% of patients may develop an immediate or delayed reaction to this form of I.V. iron.[2] These reactions may be anaphylactoid with malaise, itching, urticaria, sweating, myalgia, arthralgia and febrile episodes, or even anaphylactic with dyspnoea, hypotension and circulatory collapse.[3,4] Few if any data indicate that I.V. iron is associated with an increased risk of infections, cardiovascular disease, malignancy, or iron overload.[3–5]

Intravenous (I.V.) iron sucrose [FeS] has been used for fifty years and is generally referred to as iron saccharate or ferric saccharate. In the remainder of this manuscript the term 'I. V. iron sucrose (FeS)' solely refers to the product called Venofer (Venofer®, Vifor Inc., Switzerland).[6] The efficacy and safety of FeS has been initially demonstrated in patients with end stage renal disease indicating good safety and an efficacy profile which was paralleled by improvement in the quality of life.[7]

The anti-TNF antibody, Infliximab (IFX) has become a cornerstone immunomodulatory treatment in inflammatory bowel disease (IBD) for several indications.[8–10] IFX induces healing of mucosal ulcers[11] which could reduce intestinal iron loss and subsequently alleviate iron deficiency related anaemia (IDRA).

Recently, there have been reports on increased serum erythropoietin (EPO) levels in IBD patients compared to the healthy population.[12–14] In contrast, it has been shown that in anaemic IBD patients EPO production is inadequate in relation to the degree of anemia.[15–17]

In IDRA, the combination of soluble transferrin receptors (sTFRs) with serum ferritin allows a reliable assessment of the iron deficit.[18,19] However, in chronic inflammatory conditions such as Crohn's disease, ferritin measurement is not always a reliable index. Thus, sTFR levels provide valuable information since they are determined by cellular iron demands and erythroid proliferation rate.[20]

The VEGF (vascular endothelial growth factor) family and its receptors determine development and homeostasis of many organs, including the haematopoietic system, independent of their vascular role. We have previously shown that patients with gastrointestinal inflammatory conditions including IBD have significantly increased serum VEGF levels compared to healthy subjects.[21]

No studies so far have assessed the safety and the effect on haematopoiesis and iron stores of combined FeS and IFX treatment in anaemic IBD patients.

In this study we prospectively assessed the safety of combined IFX and FeS treatment and we investigated the serum kinetics of EPO, sTFRs and VEGF during combined therapy with IFX and FeS in a well defined cohort of IBD patients with iron deficiency anaemia.

2. Materials and methods

2.1. Study design

We conducted a prospective chart analysis of all IBD anaemic patients on IFX who received FeS during the period 2001–2004. All patients received consecutive FeS infusions to achieve a pre-calculated total dose. To avoid iron overload infusions were interrupted when the transferrin saturation exceeded 50%. The analysis was designed to assess all relevant to the treatment safety issues, to record any adverse event and to demonstrate any possible predicting factor(s) for this event.

In addition we prospectively investigated serum haematopoietic factors kinetics in 29 anaemic CD patients (19 females) on IFX induction and subsequent systematic treatment (5 mg/kg) who had also received combined FeS treatment. Data were stored in and retrieved from hospital electronic records containing all medical and laboratory data. Adverse events were specifically captured in the electronic records.

2.2. Inclusion criteria and exclusion criteria

Patients diagnosed with iron deficiency IBD-related anaemia, not administered oral iron agents for at least 2 weeks or with documented poor tolerance or unresponsiveness to oral supplementation by iron salts, with below-target range of Hb levels (<12 g/dL) and evidence of iron deficiency (Tsat<20%) were included in the study population. The minimum follow up time after FeS was set at four months.

Patients with recent severe bacterial or viral infection, anaemia of other causes (e.g. vitamin B12 deficiency, folic acid deficiency, haemolytic disorder, haemoglobinopathy), anticipated need for blood transfusion, asthma, eczema or other atopic allergy, history of drug allergy, history of previous allergic reaction to iron, pregnancy, severe cardiac, severe hepatic or renal or psychiatric disorders, and any evidence of iron overload (Tsat>50% or ferritin>800 ng/ml) were excluded. Patients receiving antihistamines or exogenous erythropoietin were also excluded.

2.3. I.V. iron sucrose protocol of administration

The cumulative dose per FeS treatment cycle was calculated using the formula: total iron deficit (mg) = W[kg] × [target Hb − actual Hb]g/l × 0.24 + depot iron (500 mg) [W = weight, Hb = haemoglobin].[22] FeS was administered on a day care basis with consecutive infusions spaced over several weeks to achieve the calculated dose. After achieving the precalculated dose and when transferrin saturation exceeded 50% FeS infusions were interrupted in order to avoid iron overload. A new FeS cycle was restarted when saturation decreased to less than 30%.[23]

Patients who were scheduled to receive IFX treatment on the same day as FeS received the IFX infusion first, followed

by a wash out with 50 ml of normal saline and finally FeS was administered using the same venous access with a maximal infusion rate of 4 mg/min.

Prior to the initiation of the first FeS infusion ever each patient received a test dose of 25 mg I.V. FeS over 15 min titrated with an infusion pump followed by monitoring of vital signs for one hour. Blood analysis was always performed before the initiation of IFX and/or FeS infusion.

2.4. Safety

All adverse events at the infusion unit were prospectively recorded. Additional minor or major adverse events were reviewed in all patients at each infusion session by physical examination and direct inquiry of patients.

In detail, hypotension was recorded as adverse event if, in the opinion of the attending physician, a decrease in blood pressure regardless of degree or absolute value was clinically significant. In case of allergic reaction the administration of FeS was interrupted and antihistamines combined with 100 mg of hydrocortisone were I.V. administered.

2.5. Data analysis

In addition to demographic data and clinical disease characteristics we recorded the total number of FeS infusions, the timing of parallel administration of FeS and IFX, as well as the mean number of infusions per patient.

Haematological parameters such as Hb, transferrin, Tsat, ferritin, were assessed prior to first FeS infusion (pre-), after the end of the cycle of infusions (post-), while changes between post- and pre-infusion values were also calculated. We also recorded the percentage of patients with Hb>12 g/dL on the four-month of follow up after iron supplementation. To examine possible non-haematopoietic effects of FeS we also determined CRP as well as routine serum biochemical parameters before the first infusion and during follow up.

In addition, Crohn's Disease Activity Index (CDAI) and quality of life assessment as measured by Inflammatory Bowel Disease Questionnaire (IBDQ), prior to first FeS infusion and after every FeS infusion cycle was retrieved from our prospective IBD database.

2.6. Kinetics of erythropoietin, VEGF and soluble transferrin receptors

We performed a prospective kinetic study of serum EPO, sTFR and VEGF levels before and after IFX introduction and during combined IFX systematic and FeS infusions according to a predefined schedule (Fig. 1).

Serum samples were available before introduction of IFX (baseline sample 1), before the initiation of the first FeS infusion (sample 2, week 0) and on week 4 (sample 3) and week 12 (sample 4) of FeS treatment. To correlate baseline endogenous EPO production to the actual degree of anaemia (Hb levels), we defined expected EPO levels based on the degree of anaemia as previously reported (Log EPO = 3.48 − 0.20*X* Hb)[14] and we calculated the ratio of observed vs. expected EPO for each patient separately. We also defined the relative increase of EPO (or sTFR) between time points 1 and 2 as the ratio (EPO2 − EPO1) / EPO1.

EPO was measured with EPO-Trac ^{125}I RIA (Diasorin, Saluggia, Italy) and sTFRs were determined with Quantikine™ IVD™ ELISA. Reference values for EPO were 8–230 mU/mL and for sTFR 18.4 nmol/l (2.5–97.5 percentiles: 8.7–28.1 nmol/l). For EPO the interassay precision is <6% at a level of 160 mU/ml and <15% at 14 mU/ml and for sTFR the interassay precision of the method is <10%.

VEGF levels were determined with a specific ELISA (R&D systems, Minneapolis MN) designed to measure the most predominant VEGF^{165} isoform with an intra-assay and the inter-assay precision (coefficient of variation) of 5.1% and 7.0% respectively.

2.7. Ethical considerations

All patients gave written informed consent for data collection in the IBD database (VLECC study).

2.8. Statistical analysis

Normally distributed continuous variables were described as means ± SD and comparisons between pre–post-FeS groups were performed using a paired sample T-test. For variables which were not normally distributed we performed Mann–Whitney test and Wilcoxon Signed Rank test, and we used the median values expressed with the interquartile range (IQR).

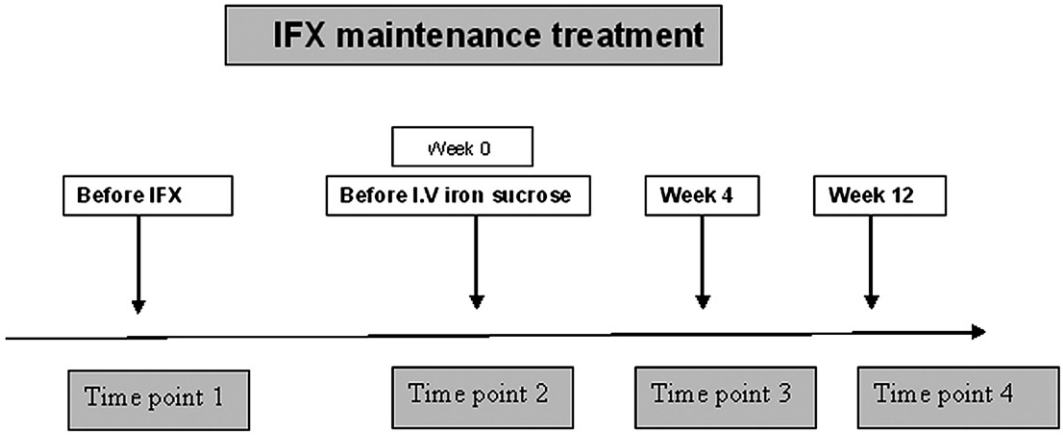

Figure 1 Time schedule of serum sampling for the serum EPO, sTFR and VEGF kinetics study during Infliximab and I.V. iron sucrose infusions.

Table 1 Demographics and clinical characteristics of IBD patients on combined infliximab (IFX) and I.V. iron sucrose (FeS) treatment

IFX groups	Sex (M/F)	Age (years ± SD)	IBD diagnosis [a] (CD/UC)	Immunosuppressant [b]
All IFX ($n=87$)	28/59	35.7 ± 11.5	72/15	77/87 (88.5%)
IFX-systematic ($n=42$)	12/30	34.2 ± 10.2	40/2	42/42 (100%)
IFX-episodic ($n=45$)	16/29	37.2 ± 12.4	32/13	35/45 (77.8%)
Kinetics study group [c]				$N=29$
Sex (M/F)				10/19
Age in years (median-IQR) [d]				26.2 (15.8–49.7)
Time (months) on IFX before FeS [median, range]				11 (0–50.4)
Concomitant azathioprine				20/29
Clinical response to IFX				21/29 (72%)
Patients with haemoglobin ≥12 g/dl after I.V. iron sucrose				23/29 (79%)
Expected endogenous EPO (mU/mL) [median, range]				19.5 [3.1–63]

[a] CD = Crohn's disease, UC = Ulcerative colitis.
[b] Azathioprine or methotrexate.
[c] Patients with Crohn's disease on IFX systematic therapy 5 mg/kg every 8 weeks.
[d] IQR = interquartile range.

X^2 analysis was used when comparing frequencies. For correlation, the Spearman Rank correlation was used. A p-value <0.05 (two-tailed) was considered to be significant. Statistical analysis was conducted using the SPPS 15.0 working package (SPSS Inc., Chicago, IL).

3. Results

3.1. Study population

Eighty-seven patients [72 Crohn's disease (CD), 15 ulcerative colitis (UC)] were included, of whom 42 patients on systematic and 45 patients on episodic IFX treatment (Table 1).

In these 87 patients, FeS was scheduled on the same day (dose 200–400 mg), immediately after IFX infusion in 37 patients (23 patients in IFX systematic, 14 patients in episodic use). In 24 patients (10 in IFX systematic, 14 in IFX episodic) the time interval between the last IFX dose to the first FeS dose was less than 12 weeks and in 26 patients (9 in IFX systematic and 17 in IFX episodic) the last IFX dose to the first FeS dose was exceeding the time interval of 12 weeks. Twenty-two (52.4%) IFX systematic patients and 21 (46.7%) IFX episodic patients reached haemoglobin levels >12 g/dl at the end of I.V. iron sucrose infusions.

Iron store kinetics and haematopoietic parameters were followed in 29/87 patients who initially received IFX induction and then were on every 8-week systematic therapy (Table 1). In this group the time interval between the last IFX dose to the first FeS dose was less than 12 weeks.

3.2. Efficacy of combined IFX and FeS therapy

In the whole group a total of 270 FeS infusions were administered (Table 2). A trend towards more patients on

Table 2 Safety and efficacy of combined I.V. iron sucrose and Infliximab treatment

Safety and efficacy parameters of combined FeS and IFX treatment	Infliximab systematic ($n=42$)	Infliximab episodic ($n=45$)	All Infliximab patients ($n=87$)
No. of patients receiving I.V. iron sucrose immediately after Infliximab infusion	23	14	37
No. of patients receiving I.V. iron sucrose <12 weeks after Infliximab infusion	10	14	24
Cumulative number of I.V. iron sucrose infusions	129	141	270
Number of I.V. iron sucrose infusions per patient (mean ± SD)	3.07 ± 0.31	3.13 ± 1.22	2.78 ± 0.89
I.V. iron sucrose dose per patient (median with / IQR)	600 [200–1000]	600 [400–1000]	600 [400–1000]
Range (min–max) of I.V. iron sucrose dose (Fe3+ mg) per infusion	200–400	200–400	200–400
No of patients (%) with haemoglobin >12 g/dl at the end of I.V. iron sucrose infusions	22 (52.4%)	21 (46.7%)	43 (49.4%)
No. of patients (%) needing new cycle of I.V. iron sucrose during follow up	24 (57.1%)	31 (68.9%)	55 (63.2%)
Short term adverse events (allergic reactions)	0	2 (4.4%)	2 (2.3%)
Long term adverse events [a]	0	1 (2.2%)	1 (1.1%)
CRP de novo increasing	12 (28.6%)	13 (28.9%)	25 (28.7%)
CRP remaining negative or decreasing	30 (71.4%)	32 (71.1%)	62 (71.3%)

[a] Low respiratory tract infection (probable).

Table 3 Kinetics of serum erythropoietin (EPO), vascular endothelial growth factor (VEGF) and soluble transferrin receptors (sTFR) in patients with Crohn's disease before and after Infliximab and during a 12-week combined I.V. iron sucrose administration

	Before IFX	Before FeS	*p*-value*	After FeS	*p*-value**
EPO (mU/mL)	24.5 (14.5–38.3)	29.0 (19.0–53.0)	0.029	20.0 (14.5–33.5)	<0.001
sTFR (nmol/L)	24.1 (16.9–34.8)	29.7 (20.5–41.7)	0.002	18.8 (14.5–27.7)	<0.001
VEGF (pg/ml)	191 (114–304)	192 (100–318)	NS	204 (73–259)	NS

Values are expressed as median (interquartile range).
p-value* = comparison of values before IFX and before FeS.
p-value** = comparison of values before and after FeS.

episodic IFX needing a new FeS cycle (68.9%) compared to IFX systematic (57.1%) was observed ($p=0.07$). Minimal and maximal daily I.V. iron sucrose dose did not differ between IFX episodic and systematic patients.

Serum iron-related parameters did not differ between the systematic and episodic IFX systematic group. Also, the median (IQR) cumulative FeS dose required to replenish stores was similar in the episodic and systematic IFX group (600 [200–1000] mg vs. 600 [400–1000] mg, $p=0.36$).

3.3. Kinetics of erythropoietin, soluble transferrin receptors and VEGF

The results of the serum kinetic study are presented in Table 3. Baseline observed EPO levels [EPO(1)] were significantly higher than expected for the actual degree of anaemia ($p=0.029$) and the ratio of observed EPO/expected EPO before the initiation of FeS treatment was 1.3 (range 0.4–10.1). We found no correlation between the EPO1 levels and the ratio of observed EPO/expected EPO with the corresponding CRP and CDAI values.

IFX resulted in a significant increase of EPO(2) and sTFR(2) levels, compared to baseline EPO(1) and sTFR(1) levels with a median (IQR) EPO and sTFR increase of 5.0 (0.0–20.0) mU/mL and 5.2 (0.8–22.9) nmol/l [$p=0.029$ and $p=0.005$ respectively] (Figs. 2 and 3).

After a 12-week period of combined FeS and IFX treatment, EPO(4) and sTFR(4) levels dropped significantly compared to the pre-FeS EPO(2) and sTFR(2) levels ($p<0.001$). Overall, the decrease in EPO levels after the initiation of FeS treatment was [median, range] −10.0 mU/mL [−20.0−0.5] and the corresponding decrease in sTFR levels was −7.1 nmol/l [−14.2−−4.3]. Both EPO and sTFR drops were below baseline levels, although not significantly different (Figs. 2 and 3).

The relative (%) decrease in sTFR during combined FeS and IFX treatment correlated with the total dose (mg) of FeS [$r=-0.705$, $p<0.001$] and the increase in Hb [$r=-0.524$, $p=0.004$], whereas no significant correlation was noticed between the relative (%) decrease in EPO levels and the Hb increase [$r=-0.294$, $p=0.136$].

EPO increase after the initiation of IFX treatment was significantly higher in the male group of patients compared to their female counterparts ($p=0.031$). By contrast, after combined FeS and IFX treatment the relative change in EPO levels was more pronounced in females ($p=0.023$). No significant differences in EPO and sTFR levels were noticed between IFX responders and non-responders.

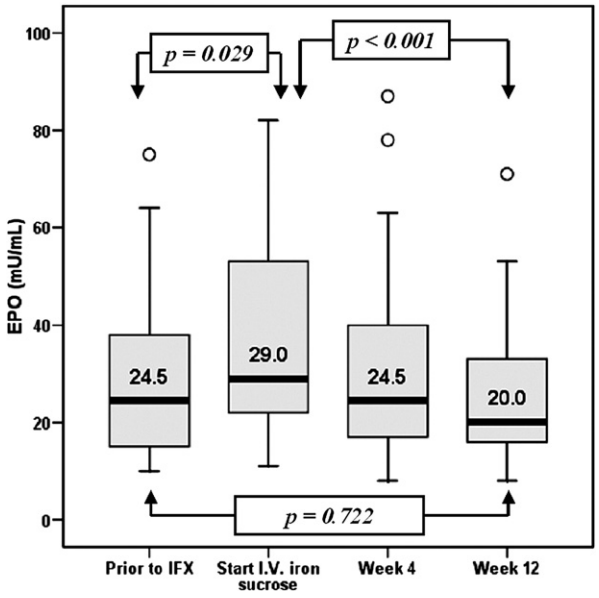

Figure 2 Serum erythropoietin levels in Crohn's disease patients before Infliximab, after Infliximab, before I.V. iron sucrose and at 12 weeks of I.V. iron sucrose treatment.

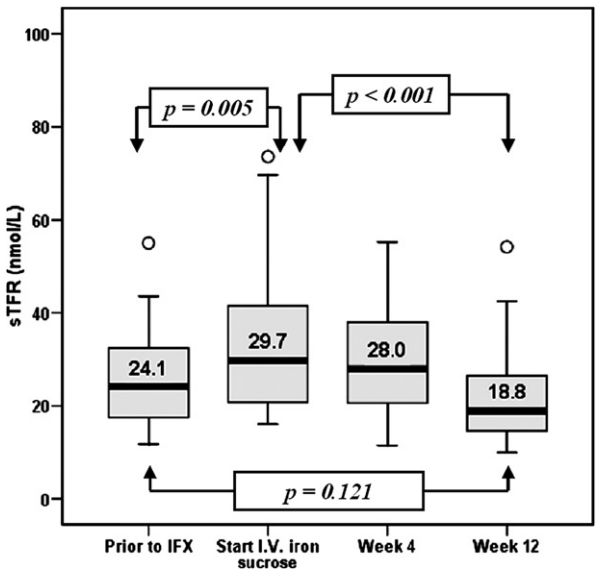

Figure 3 Serum soluble transferrin receptor levels in Crohn's disease patients before Infliximab, after Infliximab, before I.V. iron sucrose and at 12 weeks of I.V. iron sucrose treatment.

Table 4 Changes in activity indices of Crohn's disease patients on combined I.V. iron sucrose and infliximab treatment

Infliximab groups	CDAI pre [a]	CDAI post	CDAI change	IBDQ pre [b]	IBDQ post	IBDQ change
IFX-systematic ($n=42$)	213.31 ± 5.95	184.42 ± 91.31	−47.84 ± 121.22	161.39 ± 44.15	164.04 ± 30.84	5.33 ± 47.05
IFX-episodic ($n=45$)	193 ± 112.14	166.45 ± 136.38	−29.70 ± 75.91	164.00 ± 28.34	165.36 ± 38.18	−1.38 ± 31.22
All IFX ($n=87$)	205.26 ± 102.11	176.6 ± 111.59	−32.76 ± 106.29	162.41 ± 38.4	164.65 ± 34	2.76 ± 41.32

Values are expressed as mean ± SD.
[a] CDAI = Crohn's Disease Activity Index, Pre = previous to I.V. iron sucrose treatment, post = post to I.V. iron sucrose treatment, change = (post−pre) value.
[b] IBDQ = Inflammatory Bowel Disease Questionnaire.

No significant changes in VEGF levels were noted during IFX or combined FeS therapy and no significant correlation at any point of time was observed between VEGF levels and the levels of EPO, sTFRs and haemoglobin.

3.4. Adverse events

Subsequent IFX and FeS treatment in one infusion session was well tolerated. The total time of the infusion procedure (median time in the hospital for FeS I.V. only 120 min, range 90−240) was acceptable by the great majority of the patients. In none of the IFX-treated patients an early or late adverse reaction to IFX had ever been recorded previously and none of these patients had ever been receiving any kind of special pre-medication prior to each IFX infusion.

No adverse reaction occurred during I.V. iron sucrose 25-mg test dose. Adverse events considered possibly or probably related to I.V. iron sucrose administration were recorded in 2 female patients [2.3% of patients, 0.7% of infusions] both on IFX episodic therapy. In detail, one patient had nausea and skin rash during a 200 mg infusion and the other patient developed diffuse urticaria during a 400 mg infusion. In the first case infusion was not interrupted while in the second case the infusion was truncated at 300 mg.

One patient was hospitalized two weeks after the end of a FeS cycle with an episode of fever and dyspnoea and a differential diagnosis of a lower respiratory tract infection or delayed hypersensitivity to episodic IFX. The patient was treated with antibiotics only and discharged few days later in excellent condition. No other patient in this cohort reported late adverse events during the 4-month follow up.

De novo CRP increase between post- and pre-FeS infusion time points occurred in 25 out of 87 patients (28.7%) while in the remaining 62 patients (71.3%) CRP remained negative or even decreased during FeS.

We recorded no cases of bacterial infection and no septicaemia cases related to infection via indwelling catheters. CDAI and IBDQ scores were available for patients via the prospective IFX infusion program database. No significant changes in disease activity [CDAI (−32.76 ± 106.29)] or quality of life [IBDQ scores (2.76 ± 41.32)] were recorded after completion of the full course of FeS infusions (Table 4).

4. Discussion

The results of this study indicate that IFX and FeS work through different mechanisms on haematopoiesis. We demonstrate that patients with IBD and anaemia have functional iron deficiency rather than anaemia of chronic disease. Restoration of the inflammatory process with IFX even increases the need for rapidly accessible iron stores, which is alleviated by replenishing the stores with IV iron. Furthermore, although the safety of FeS in IBD had been demonstrated by a limited number of studies from referral IBD centers,[5,23–27] our study confirms the safety of FeS and adds the experience with combined FeS and IFX treatment in anaemic IBD patients. The differential effects of combined IFX and FeS treatment in these haematopoiesis related indices such as EPO and sTFR may be implemented to further advance the management of IDRA in patients with IBD.

First, we confirmed that patients with CD and IDRA have higher than expected endogenous EPO levels indicating that EPO increase is strongly related to CD anaemia and that our patients were resistant to endogenous EPO production. It is possible that failure of bone marrow to respond to increased EPO levels leads to further incremental EPO production. Interestingly, serum EPO levels have been reported to depend not only on the Hb concentration but also on the proliferative activity of red blood cells and on bone marrow responsiveness.[28–30]

Azathioprine use has been related to an increased endogenous EPO production in renal transplant recipients[31,32] probably as a compensatory phenomenon to bone marrow suppression and ineffective erythropoiesis.[33–35] Normalization for the effect of azathioprine in our study was not possible since the vast majority of our patients were treated with azathioprine.

Secondly, we demonstrated that IFX significantly increases serum EPO, sTFR and VEGF levels. Circumstantial evidence suggests that increased local TNF-α production in the bone marrow microenvironment may be implicated in the pathogenesis of anaemia of chronic disease.[36] In fact, animals treated with TNF-α develop anaemia with anaemia of chronic disease characteristics and one could argue that anti-TNFa treatment should resolve anaemia of chronic disease.[37] Although there is a single report on a patient with CD associated anaemia refractory to conventional treatment, which resolved with the administration of IFX[38] and a report of two myelodysplastic syndrome patients in whom IFX administration resulted in sustained erythroid responses[39] we believe that our study strongly implicates that IFX per se does not increase haemoglobin levels in CD patients but by restoring haematopoiesis IFX even increases functional iron deficiency resulting in an increased demand for appropriate iron substitution.

During this 12-week kinetic study, FeS following IFX treatment restored functional iron deficiency as reflected by the decrease of serum EPO and sTFR levels, thus

indicating that IFX and FeS impact IDRA through two different pathways. The sTFR kinetics significantly correlated with changes in haemoglobin, thus immediately reflecting the efficacy of combined IFX and FeS administration. All these data taken together indicate that the relative change in sTFR levels compared to the relative change in EPO levels represents a more sensitive marker of the efficacy of FeS therapy than Hb levels.

The significantly higher increase of EPO in males compared to females after IFX administration and the more pronounced relative change of EPO after FeS administration in females points towards the hypothesis that CD related anaemia in males is more related to chronic disease while in females iron deficiency remains the predominant cause. However, this hypothesis has to be further confirmed.

Finally, in both transgenic mouse and primate models an inhibitory effect of endogenous VEGF on EPO production has been suggested.[40] However, in this study we did not observe such a correlation between EPO and VEGF levels.

To the best of our knowledge, this is the first study in IBD anaemic patients demonstrating that FeS and IFX can be successfully administered in combination with good tolerance, efficacy and overall safety. Our cohort was composed of a rather 'difficult to treat group', mainly consisting of young women with refractory disease in need of infliximab therapy. In fact, women older than 50 years of age significantly decrease their iron store deficit due to menopause. In previous clinical studies with anaemic IBD patients, FeS infusions have been given using 200 mg FeS 3 times per week.[24] In our study a more 'naturalistic' approach was followed and FeS infusions were scheduled with variable intervals to accommodate the predominantly active professionals in our cohort. For patients combined infliximab and IV iron infusions sessions limit the burden of the therapy on their activities of daily live.

Only 2/87 patients experienced an infusion related adverse event, which was easily managed. Side effects from FeS have been occasionally reported. According to a large post-marketing study the incidence of anaphylactic reactions may be as low as 2/100,000 infusions.[3] We did not observe any anaphylactic reaction in this cohort and in general, tolerability was excellent. The side effects observed in two patients with immediate reactions may have been caused by the toxic effect of excess iron released by unstable iron complexes.[41] In the additional patient a delayed reaction to IFX or a respiratory infection was a more likely cause. Interestingly all three patients were on episodic IFX treatment. Systemic reactions to free iron appear to be related to the dose and rapidity of administration. The maximal recommended dosage of FeS is 600 mg/week or 7 mg/kg and the maximum infusion rate is 20 mg/min.[6] Those upper limits were not exceeded in any of our patients.

A test dose was applied prior to the first infusion following guidelines of iron sucrose administration, although it has been suggested that FeS may be safely administered without a prior test dose.[42] Although a test dose does not exclude adverse reactions we strongly believe as others[43] that a history of drug allergy and low body mass[44] are significant predictors of adverse reactions to IV FeS. In these patients, dose and infusion speed should be adjusted to avoid free iron toxicity given that there is no study on the possible impact of IFX on the pharmacokinetics of FeS in patients. Interestingly, all of our patients with an adverse reaction had a body weight lower than 55 kg.

High serum iron levels are generally believed to increase oxidative stress and may be pro-inflammatory. A recent prospective study enrolling 19 CD patients with iron deficiency anaemia demonstrated that oral ferrous fumarate but not intravenous FeS, increased clinical disease activity in IBD patients.[26] In this study no significant changes in the IBDQ score were observed before and after the completion of FeS infusions and, if anything, a decrease in CDAI during FeS infusions was found. The absence of a pro-inflammatory effect is further supported by the CRP trends in the study; Mean CRP levels were not increased after FeS treatment and only a quarter of our patients had de novo CRP increase during FeS infusions. In contrast to a recent study[45] showing a significant CDAI improvement 6 weeks after oral iron sulphate or FeS treatment, in our cohort the decrease in CDAI did not reach statistical significance probably due to the fact that a great proportion of our patients were already in remission before starting FeS infusions.

An association between prolonged use of I.V. iron and excess incidence of neoplasia, infection and cardiac disease has been suggested.[46] We recorded only one case of a probable lower respiratory tract infection. Long-term follow up studies need to be designed in order to assess the real additional risk for cardiac disease and extra-intestinal infections in IBD patients frequently receiving FeS infusions combined with any other kind of treatment.[47–51]

To conclude, IFX and FeS combined treatment can be successively administered with excellent tolerability in IBD patients. The kinetic study on haematopoietic parameters in anaemic patients with Crohn's disease showed that IFX administration increases functional iron deficiency, which is restored after a combined I.V. iron sucrose treatment.

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